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(54) Title: CONJUGATES USEFUL IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

(57) Abstract

Novel pharmaceutical compositions useful for the treatment of benign prostatic hyperplasia which comprises novel oligopeptides, which are selectively cleaved by enzymatically active PSA, in conjugation with a cytotoxic agent are described. Methods of treating benign prostate hypertrophy are also disclosed.

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TITLE OF THE INVENTION

CONJUGATES USEFUL IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

BACKGROUND OF THE INVENTION

Benign prostate hyperplasia (or "prostatism") can be seen in almost 100 percent of all men over the age of 80, and changes in the prostate can be discovered in about 50 percent of men by the time they reach the age of 60. Many men with benign prostate hyperplasia (BPH) remain without symptoms, others show slow progression, while others remain stable. However, some 400,000 men a year have symptoms severe enough to require surgery. The most common surgery, transurethral resection, is effective in relieving the symptoms of BPH, although side-effects, including morbidity from the operation itself, mild to severe urinary incontinence and some degree of erectile or ejaculatory dysfunction, have been reported in a limited number of patients.

Normally the prostate remains stable until after the age of 45, when the tissue begins to change, growing and causing the size of the prostate to increase. The enlarging prostate squeezes the urethra, producing the symptoms that characterize BPH. These include difficulty in starting urination (hesitancy), a weak urinary stream, dribbling after urination, and increased frequency or urgency to urinate during the sleep period. Sometimes urination may be painful. The symptoms of obstruction of the urethra can often become more severe if a urinary infection develops. one of the common complications of BPH.

Prostate specific Antigen (PSA) is a single chain 33 kDa glycoprotein that is produced almost exclusively by the human prostate epithelium and occurs at levels of 0.5 to 2.0 mg/ml in human seminal fluid (Nadji, M., Taber, S.Z., Castro, A., et al. (1981) Cancer 48:1229;Papsidero, L., Kuriyama, M., Wang, M., et al. (1981). JNCI 66:37; Qui, S.D., Young, C.Y.F., Bihartz, D.L., et al. (1990), J. Urol. 144:1550; Wang, M.C., Valenzuela, L.A., Murphy, G.P., et al. (1979). Invest. Urol. 17:159). The single carbohydrate unit is attached at asparagine residue number 45 and accounts for 2 to 3 kDa of the total

molecular mass. PSA is a protease with chymotrypsin-like specificity (Christensson, A., Laurell, C.B., Lilja, H. (1990). Eur. J. Biochem. 194:755-763). It has been shown that PSA is mainly responsible for dissolution of the gel structure formed at ejaculation by proteolysis of the major proteins in the sperm entrapping gel, Semenogelin I and Semenogelin II, and fibronectin (Lilja, H. (1985). J. Clin. Invest. 76:1899; Lilja, H., Oldbring, J., Rannevik, G., et al. (1987). J. Clin. Invest. 80:281; McGee, R.S., Herr, J.C. (1988). Biol. Reprod. 39:499). The PSA mediated proteolysis of the gel-forming proteins generates several soluble Semenogelin I and Semenogelin II fragments and soluble fibronectin fragments with liquefaction of the ejaculate and release of progressively motile spermatoza (Lilja, H., Laurell, C.B. (1984). Scand. J. Clin. Lab. Invest. 44:447; McGee, R.S., Herr, J.C. (1987). Biol. Reprod. 37:431). Furthermore, PSA may proteolytically degrade IGFBP-3 (insulin-like growth factor binding protein 3) allowing IGF to stimulate specifically the growth of PSA secreting cells (Cohen et al., (1992) J. Clin. Endo. & Meta. 75:1046-1053).

PSA complexed to alpha 1 - antichymotrypsin is the predominant molecular form of serum PSA and may account for up to 95% of the detected serum PSA (Christensson, A., Björk, T., Nilsson, O., et al. (1993). J. Urol. 150:100-105; Lilja, H., Christensson, A., Dahlén, U. (1991). Clin. Chem. 37:1618-1625; Stenman, U.H., Leinoven, J., Alfthan, H., et al. (1991). Cancer Res. 51:222-226). The prostatic tissue (normal, benign hyperplastic, or malignant tissue) is implicated to predominantly release the mature, enzymatically active form of PSA, as this form is required for complex formation with alpha 1 - antichymotrypsin (Mast, A.E., Enghild, J.J., Pizzo, S.V., et al. (1991). Biochemistry 30:1723-1730; Perlmutter, D.H., Glover, G.I., Rivetna, M., et al. (1990). Proc. Natl. Acad. Sci. USA 87:3753-3757). Therefore, in the microenvironment of prostatic PSA secreting cells, the PSA is believed to be processed and secreted in its mature enzymatically active form not complexed to any inhibitory molecule. PSA also forms stable complexes with alpha 2 - macroglobulin, but as this results in encapsulation of PSA and complete loss of the PSA epitopes, the in vivo

significance of this complex formation is unclear. A free, noncomplexed form of PSA constitutes a minor fraction of the serum PSA (Christensson, A., Björk, T., Nilsson, O., et al. (1993). J. Urol. 150:100-105; Lilja, H., Christensson, A., Dahlén, U. (1991). Clin. Chem. 37:1618-1625). The size of this form of serum PSA is similar to that of PSA in seminal fluid (Lilja, H., Christensson, A., Dahlén, U. (1991). Clin. Chem. 37:1618-1625) but it is yet unknown as to whether the free form of serum PSA may be a zymogen; an internally cleaved, inactive form of mature PSA; or PSA manifesting enzyme activity. However, it seems unlikely that the free form of serum PSA manifests enzyme activity, since there is considerable (100 to 1000 fold) molar excess of both unreacted alpha 1 - antichymotrypsin and alpha 2 - macroglobulin in serum as compared with the detected serum levels of the free 33 kDa form of PSA (Christensson, A., Björk, T., Nilsson, O., et al. (1993). J. Urol. 150:100-105; Lilja, H., Christensson, A., Dahlén, U. (1991). Clin. Chem. 37:1618-1625).

Serum measurements of PSA are useful for monitoring the treatment of adenocarcinoma of the prostate (Duffy, M.S. (1989). Ann. Clin. Biochem. 26:379-387; Brawer, M.K. and Lange, P.H. (1989). Urol. Suppl. 5:11-16; Hara, M. and Kimura, H. (1989). J. Lab. Clin. Med. 113:541-548). Above normal serum concentrations of PSA have also been reported in benign prostatic hyperplasia and subsequent to surgical trauma of the prostate (Lilja, H., Christensson, A., Dahlén, U. (1991). Clin. Chem. 37:1618-1625). Therefore, a cytotoxic compound that could be activated by the proteolytic activity of PSA should be prostate cell specific as well as specific for PSA secreting prostate metastases. Such a specific agent may be effective against BPH without causing the side-effects associated with other therapies.

Accordingly, it is the object of this invention to provide a novel pharmaceutical composition useful for the treatment of benign prostatic hyperplasia which comprises novel oligopeptides, which are selectively cleaved by enzymatically active PSA, in conjugation with a cytotoxic agent.

Another object of this invention is to provide a method of treating benign prostatic hyperplasia which comprises administration of the novel pharmaceutical composition.

SUMMARY OF THE INVENTION

Novel pharmaceutical compositions useful for the treatment of adverse conditions of the prostate, in particular benign prostatic hyperplasia, which comprise novel oligopeptides, which are selectively cleaved by enzymatically active PSA, in conjugation with a pharmaceutical agent are described. Methods of treating such conditions of the prostate are also disclosed.

BRIEF DESCRIPTION OF THE FIGURES

FIGURES 1 and 1A: *Primary Amino Acid Sequence of Semenogelin I:* The primary amino acid sequence of Semenogelin I is shown. (SEQ.ID.NO.: 1) The PSA proteolytic cleavage sites ("CS") are shown (numbered in order of the relative affinity of a site towards PSA hydrolysis) and the protein fragments are numbered sequentially starting at the amino terminus.

FIGURE 2: *Cleavage Affinity of Synthetic Oligopeptides:* A nested set of synthetic oligopeptides was prepared and the oligopeptides were digested with enzymatically active free PSA for various times. The results are shown in Table 2. All of the oligopeptides were tested as trifluoroacetate salts.

FIGURES 3, 3A and 3B: *Cleavage Affinity of Synthetic Oligopeptides:* Synthetic oligopeptides were prepared and the oligopeptides were digested with enzymatically active free PSA for four (4) hours. The percentage of the oligopeptide that is cleaved in this period of time is listed. The results are shown in Table 4. Table 4a shows the amount of time (in minutes) required for 50% cleavage of the noted oligopeptides with enzymatically active free PSA. If no salt is indicated for an oligopeptide, the free base was tested.

FIGURE 4: *Cytotoxicity Data of Non-cleavable Oligopeptide-Doxorubicin Conjugates:*
The data of the figure shows comparative cytotoxicity of doxorubicin and a conjugate of doxorubicin covalently bound to an oligopeptide (Compound 12d) that does not contain the free PSA proteolytic cleavage site. The EC_{50} for doxorubicin is 0.3μM, while the acetylated oligopeptide modified doxorubicin has an EC_{50} that has been reduced by greater than 300 fold. This conjugate had no HPLC detectable contamination with unmodified doxorubicin. The oligopeptide alone had no detectable cell killing activity.

FIGURES 5 and 5A: *Cleavage Affinity of Oligopeptides in Conjugation with Doxorubicin by Free PSA In Vitro:*
Oligopeptides-doxorubicin conjugates were prepared and the conjugates were digested with enzymatically active free PSA for four (4) hours. The percentage conjugate that is enzymatically cleaved in the oligopeptide in this period of time is listed. The results are shown in Table 5. Table 5a shows the amount of time (in minutes) required for 50% cleavage of the noted oligopeptide-cytotoxic agent conjugates with enzymatically active free PSA. If no salt is indicated for the conjugate, the free conjugate was tested.

FIGURE 6: *Cleavage Affinity of Oligopeptides in Conjugation with Doxorubicin in Cell Conditioned Media:*
Oligopeptides-doxorubicin conjugates were reacted for four (4) hours with cell culture media that had been conditioned by exposure to LNCaP cells (which are known to secrete free PSA) or DuPRO cell (which do not secrete free PSA). The percentage conjugate that is enzymatically cleaved in the oligopeptide in this period of time is listed. The results are shown in Table 6.

FIGURE 7: *Cytotoxicity Data of Cleavable Oligopeptide-Doxorubicin Conjugates:*

The data in Table 7 shows cytotoxicity (as EC_{50}) of conjugates of doxorubicin covalently bound to an oligopeptide that contain a free PSA proteolytic cleavage site against a cancer cell line that is known to secrete free PSA. Also shown for selected conjugates is the cytotoxicity of the conjugate against a cell line (DuPRO) which does not secrete free PSA. If no salt is indicated for the conjugate, the free conjugate was tested.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to pharmaceutical compositions that comprise conjugates that contain oligopeptides, which are specifically recognized by the free prostate specific antigen (PSA) and are capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen, and pharmaceutical agents covalently linked to such oligopeptides directly or through a linker unit, or pharmaceutically acceptable salts thereof. In particular, this invention is directed to such conjugates wherein the pharmaceutical agent is a cytotoxic agent. The present invention also relates to a novel method of treating adverse conditions of the prostate, in particular benign prostatic hyperplasia, which utilizes these compositions.

Such oligopeptides include oligomers that comprise an amino acid sequence selected from:

a) AsnLysIleSerTyrGlnlSer (SEQ.ID.NO.: 13),

b) LysIleSerTyrGlnlSer (SEQ.ID.NO.: 14),

c) GlyGluAsnGlyValGlnLysAspValSerGlnXaaSerIleTyrlSerGlnThrGlu (SEQ.ID.NO.: 15),

d) GlyLysGlyIleSerSerGlnTyrlSerAsnThrGluGluArgLeu (SEQ.ID.NO.: 2),

e) AsnLysIleSerTyrTyrlSer (SEQ.ID.NO.: 127),

f) AsnLysAlaSerTyrGlnlSer (SEQ.ID.NO.: 128),

g) SerTyrGlnlSerSer (SEQ.ID.NO.: 129);

h) LysTyrGlnlSerSer (SEQ.ID.NO.: 140);

i) hArgTyrGlnlSerSer (SEQ.ID.NO.: 141);

j) hArgChaGlnlSerSer (SEQ.ID.NO.: 185); and

k) TyrGlnlSerSer (SEQ.ID.NO.: 186);

wherein hArg is homoarginine, Cha is cyclohexylalanine and Xaa is any natural amino acid.

In an embodiment of the instant invention, the oligopeptides include oligomers that comprise an amino acid sequence that is selected from:

a) AsnLysIleSerTyrGlnlSerSer (SEQ.ID.NO.: 16),

b) AsnLysIleSerTyrGlnlSerAla (SEQ.ID.NO.: 130),

c) AsnLysIleSerTyrGlnlSerSerSer (SEQ.ID.NO.: 17),

d) AlaAsnLysIleSerTyrGlnlSerSerSer (SEQ.ID.NO.: 18),

e) LysIleSerTyrGlnlSerSerSerThrGlu (SEQ.ID.NO.: 19),

f) GlyGluAsnGlyValGlnLysAspValSerGlnArgSerIleTyrlSerGlnThrGlu (SEQ.ID.NO.: 4),

g) GlyGluAsnGlyValGlnLysAspValSerGlnSerSerIleTyrlSerGlnThrGlu (SEQ.ID.NO.: 5),

h) AlaAsnLysIleSerTyrTyrlSer (SEQ.ID.NO.: 131),

i) AlaAsnLysAlaSerTyrGlnlSer (SEQ.ID.NO.: 132),

j) SerTyrGlnlSerSerThr (SEQ.ID.NO.: 133),

k) SerTyrGlnlSerSerSer (SEQ.ID.NO.: 134),

l) LysTyrGlnlSerSerSer (SEQ.ID.NO.: 142),

m) hArgTyrGlnlSerSerSer (SEQ.ID.NO.: 143), and

n) SerTyrGlnlSerSerLeu (SEQ.ID.NO.: 135);

or the pharmaceutically acceptable salt thereof.

In a more preferred embodiment of the instant invention, the oligopeptides include oligomers that comprise an amino acid sequence that is selected from:

a) AsnLysIleSerTyrGln lSerSerSerThr (SEQ.ID.NO.: 10),

b) AlaAsnLysIleSerTyrGlnlSerAla (SEQ.ID.NO.: 136),

c) AsnLysIleSerTyrGlnlSerSerSerThrGlu (SEQ.ID.NO.:3),

d) AlaAsnLysIleSerTyrGlnlSerSerSerThrGlu (SEQ.ID.NO.: 11),

e) GlyGluAsnGlyValGlnLysAspValSerGlnArgSerIleTyrlSerGlnThrGlu (SEQ.ID.NO.: 4),

f) AlaAsnLysIleSerTyrTyrlSerSer (SEQ.ID.NO.: 137),

g) AlaAsnLysIleSerTyrTyrlSerAla (SEQ.ID.NO.: 138),

h) AlaAsnLysAlaSerTyrGlnlSerAla (SEQ.ID.NO.: 139),

i) AlaSerTyrGlnlSerSerLeu (SEQ.ID.NO.: 94);

or the pharmaceutically acceptable salt thereof.

In a further embodiment of the instant invention, the oligopeptides include oligomers that comprise an amino acid sequence that is selected from:

a) GlyArgLysAlaAsnLysIleSerTyrGlnlSerSerSerThrGluGluArgArg LeuHisTyr GlyGluAsnGly (SEQ.ID.NO.: 6).

The phrase "oligomers that comprise an amino acid sequence" as used hereinabove, and elsewhere in the Detailed Description of the Invention, describes oligomers of from about 6 to about 100 amino acids residues which include in their amino acid sequence the specific amino acid sequence decribed and which are therefore proteolytically cleaved within the amino acid sequence described by free PSA. Thus, for example, the following oligomer: GlnLeuAspAsnLysIleSerTyrGlnlSerSerSerThrHisGlnSerSer (SEQ.ID.NO.: 20) comprises the amino acid sequence: AsnLysIleSerTyrGlnlSerSerSerThr (SEQ.ID.NO.:10) and would therefore come within the instant invention. It is understood that such oligomers do not include semenogelin I and semenogelin II.

It is also understood that the instant invention includes oligomers wherein the N-terminus amino acid or the C-terminus amino acid, or both terminus amino acids are modified. Such modifications include, but are not limited to, acylation of the amine group at the N-terminus and formation of an amide to replace the carboxylic acid at the C-terminus. Addition of such moieties may be performed during solid-phase synthesis of the oligomer; thus, attachment of the C-terminus

amino acid to a solid phase resin may be through an amine which results in an amide moiety upon acidic cleavage of the oligomer from the resin. Thus the following compounds are considered "oligomers that comprise an amino acid sequence" as used hereinabove and are meant to be illustrative and are not limiting:

AlaAsnLysIleSerTyrGlnlSerSerSerThrGlu-amide (SEQ.ID.NO.: 11)
Ac-AlaAsnLysIleSerTyrGlnlSerSerSerThrLeu (SEQ.ID.NO.: 70)

Ac-AlaAsnLysIleSerTyrGlnlSerSerSerThrGlu-amide (SEQ.ID.NO.: 11)
Ac-AlaAsnLysIleSerTyrGlnlSerSerSerThrLeu-amide (SEQ.ID.NO.: 70)
Ac-AlaAsnLysIleSerTyrGlnlSerAlaSerThrGlu-amide (SEQ.ID.NO.: 73)
Ac-AlaAsnLysIleSerTyrGlnlSerSerLysThrGlu-amide (SEQ.ID.NO.: 74)
Ac-AlaAsnLysIleSerTyrGlnlSerSerThrGlu-amide (SEQ.ID.NO.: 75)
Ac-AlaAsnLysIleSerTyrGlnlSerSerGlnThrGlu-amide (SEQ.ID.NO.: 78)
Ac-AlaAsnLysIleSerTyrGlnlSerAlaLysThrGlu-amide (SEQ.ID.NO.:79)
Ac-AlaAsnLysIleSerTyrGlnlSerThrGlu-amide (SEQ.ID.NO.: 81)
Ac-AlaAsnLysSerTyrGlnlSerSerThrGlu-amide (SEQ.ID.NO.: 82)
Ac-AlaAsnLysAlaSerTyrGlnlSerAlaSerThrGlu-amide (SEQ.ID.NO.: 84)
Ac-AlaAsnGluIleSerTyrGlnlSerAlaSerThrGlu-amide (SEQ.ID.NO.: 85)
Ac-AsnLysIleSerTyrGlnlSerSer-amide (SEQ.ID.NO.: 16)
Ac-LysIleSerTyrGlnlSerSer-amide (SEQ.ID.NO.: 86)
Ac-SerTyrGlnlSerSerThrGlu-amide (SEQ.ID.NO.: 87)
Ac-AlaSerTyrGlnlSerSerThrGlu-amide (SEQ.ID.NO.: 89)
Ac-AlaAsnLysIleSerTyrTyrlSerSerSerThrGlu-amide (SEQ.ID.NO.: 92)
Ac-AlaAsnLysIleSerTyrTyrlSerAlaSerThrGlu-amide (SEQ.ID.NO.: 93)
Ac-AlaSerTyrGlnlSerSerLeu-amide (SEQ.ID.NO.: 94)
Ac-AlaAsnSerTyrGlnlSerSerSerThrGlu-amide (SEQ.ID.NO.: 95)
Ac-AlaSerTyrGlnlSerSerSerThrGlu-amide (SEQ.ID.NO.: 96)
Ac-SerTyrGlnlSerSerSerThrGlu-amide (SEQ.ID.NO.: 97)
Ac-AlaAsnLysAlaSerTyrGlnlSerAlaSerCys-amide (SEQ.ID.NO.: 98)
Ac-hArg(Cha)GlnlSerNle-Acid (SEQ.ID.NO.: 147)
Ac-hArghTyrGlnlSerSerNle-Acid (SEQ.ID.NO.: 148)

Ac-hArgh(Cha)GlnlSerSerNle-Acid (SEQ.ID.NO.: 149)
Ac-AlaAspLysAlaSerTyrGlnlSerSer-Cha-NHNH2 (SEQ.ID.NO.: 150)
Ac-hArgTyrGlnlSerSerPro-Acid (SEQ.ID.NO.: 151)
Ac-hArgTyrGlnlSerSerHis-Acid (SEQ.ID.NO.:152)
Ac-hArgTyrGlnlSerAsn-Acid (SEQ.ID.NO.: 153)
Ac-hArgTyrGlnlSerSerSerNle-Acid (SEQ.ID.NO.: 154)
Ac-(Amf)TyrGlnlSerSerSerNle-Acid (SEQ.ID.NO.: 155)
H2NCO-hArgTyrGlnlSerSerSerLeu-Acid (SEQ.ID.NO.: 156)
Ac-AlaAspLysAlaLysTyrGlnlSerSer(Cha)-NHNH2 (SEQ.ID.NO.: 157)
Ac-(DPL)TyrGlnlSerSerSerNle-Acid (SEQ.ID.NO.: 158)
Ac-(imidazole)LysTyrGlnlSerSerLeu-Acid (SEQ.ID.NO.: 159)
Ac-AlaAspLysAla(hArg)TyrGlnlSerSerLeu-Acid (SEQ.ID.NO.: 160)
Ac-(p-NH2-Cha)TyrGlnlSerSerSerNle-Acid (SEQ.ID.NO.: 161)
Ac(imidazolyl)LysTyrGlnlSerSerSerNle-Acid (SEQ.ID.NO.: 162)
Ac-hArg(Cha)GlnlSerSerSerNle-Acid (SEQ.ID.NO.: 163)
Ac-hArgTyrGlnlSerSerSerhArg-Acid (SEQ.ID.NO.: 164)
Ac-hArgTyrGlnlSerSerSer(MeLeu) (SEQ.ID.NO.: 188)
Ac-hArgTyrGlnlSerSerSer(Ethylester-Leu) (SEQ.ID.NO.: 156)
Ac-AlaAspLysAla(imidazoleLys)TyrGlnlSerSerNle-Acid (SEQ.ID.NO.: 165)
Ac-hArg(3-Iodo-Tyr)GlnlSerSerSerNle-Acid (SEQ.ID.NO.: 166)
Ac-hArg(Me2PO3-Tyr)GlnlSerSerSerNle-Acid (SEQ.ID.NO.: 167)
Ac-hArgTyrGlnlSerSerAsp-Acid (SEQ.ID.NO.: 168)
Ac-hArg(O-Me-Tyr)GlnlSerSerSerNle-Acid (SEQ.ID.NO.: 169)
Ac-AlaAspLysAlaLysTyrGlnlSerSerNle-Acid (SEQ.ID.NO.: 170)
Ac-hArg(Cha)GlnlSerSerSer(ethylester-Leu) (SEQ.ID.NO.: 171)
Ac-(imidazolyl)Lys(Cha)GlnlSerSerSerNle-Acid (SEQ.ID.NO.: 172)
Ac-hArg(Cha)GlnlSerSerSer-Acid (SEQ.ID.NO.: 173)
Ac-hArg(Cha)GlnlSerSerNle-Acid (SEQ.ID.NO.: 174)
Ac-hArg(Cha)GlnlSerProNle-Acid (SEQ.ID.NO.: 175) and
Ac-hArg(m-fluoro-Tyr)GlnlSerSerSerNle-Acid (SEQ.ID.NO.: 176),

or the pharmaceutically acceptable salt thereof.

A person of ordinary skill in the peptide chemistry art would readily appreciate that certain amino acids in a biologically active oligopeptide may be replaced by other homologous, isosteric and/or isoelectronic amino acids wherein the biological activity of the original oligopeptide has been conserved in the modified oligopeptide. Certain unnatural and modified natural amino acids may also be utilized to replace the corresponding natural amino acid in the oligopeptides of the instant invention. Thus, for example, tyrosine may be replaced by 3-iodotyrosine, 2-methyltyrosine, 3-fluorotyrosine, 3-methyltyrosine and the like. Further for example, lysine may be replaced with N'-(2-imidazolyl)lysine and the like. The following list of amino acid replacements is meant to be illustrative and is not limiting:

Original Amino Acid	Replacement Amino Acid(s)
Ala	Gly
Arg	Lys, Ornithine
Asn	Gln
Asp	Glu
Glu	Asp
Gln	Asn
Gly	Ala
Ile	Val, Leu, Met, Nle
Leu	Ile, Val, Met, Nle
Lys	Arg, Ornithine
Met	Leu, Ile, Nle, Val
Ornithine	Lys, Arg
Phe	Tyr, Trp
Ser	Thr
Thr	Ser
Trp	Phe, Tyr
Tyr	Phe, Trp
Val	Leu, Ile, Met, Nle

Thus, for example, the following oligopeptides may be synthesized by techniques well known to persons of ordinary skill in the art and would be expected to be proteolytically cleaved by free PSA:

AsnArgIleSerTyrGln|Ser (SEQ.ID.NO.: 21)
AsnLysValSerTyrGln|Ser (SEQ.ID.NO.: 22)
AsnLysMetSerTyrGln|SerSer (SEQ.ID.NO.: 23)
AsnLysLeuSerTyrGln |SerSer (SEQ.ID.NO.: 24)
AsnLysIleThrTyrGln|SerSerSer (SEQ.ID.NO.: 25)
AsnLysIleSerPheGln|SerSerSer (SEQ.ID.NO.: 26)
AsnLysIleSerTrpGln|SerSerSerThr (SEQ.ID.NO.: 27)
AsnLysIleSerTyrAsn|SerSerSerThr (SEQ.ID.NO.: 28)
AsnLysIleSerTyrGln|ThrSerSerThr (SEQ.ID.NO.: 29)
AsnLysIleSerTyrGln|Ser (SEQ.ID.NO.: 30)
GlnLysIleSerTyrGln|SerSer (SEQ.ID.NO.: 31)
AsnArgIleThrTyrGln|SerSerSer (SEQ.ID.NO.: 32)
AsnArgIleSerPheGln|SerSerSerThr (SEQ.ID.NO.: 33)
AsnArgIleSerTrpGln|SerSerSerThr (SEQ.ID.NO.: 35)
AsnArgIleSerTyrGln|ThrSerSerThr (SEQ.ID.NO.: 36)
AsnLysIleThrTyrGln|ThrSerSerThr (SEQ.ID.NO.: 37)
AsnLysLeuSerTyrGln|ThrSerSerThr (SEQ.ID.NO.: 38)
GlnLysLeuSerTyrGln|SerSerSerThr (SEQ.ID.NO.: 39)
AsnArgLeuSerTyrGln|ThrSerSerThr (SEQ.ID.NO.: 40)
AsnLysValSerPheGln|SerSerSerThr (SEQ.ID.NO.: 41)
AsnArgValSerTrpGln|SerSerSerThr (SEQ.ID.NO.: 42)
GlnLysValSerTyrGln|SerSerSerThr (SEQ.ID.NO.: 43)
GlnLysIleSerTyrGln|ThrSerSerThr (SEQ.ID.NO.: 34)
AsnLysIleSerTyrGln|SerSerSerThr (SEQ.ID.NO.: 44);

or the pharmaceutically acceptable salt thereof.

Similarly, the following oligopeptides may be synthesized by techniques well known to persons of ordinary skill in the art and would be expected to be proteolytically cleaved by free PSA:

GlyGluGlnGlyValGlnLysAspValSerGlnSerSerIleTyrlSerGlnThrGlu (SEQ.ID.NO.: 45),
GlyGluAsnGlyLeuGlnLysAspValSerGlnSerSerIleTyrlSerGlnThrGlu (SEQ.ID.NO.: 47),
GlyGluAsnGlyValAsnLysAspValSerGlnSerSerIleTyrlSerGlnThrGlu (SEQ.ID.NO.: 48),
GlyGluAsnGlyValGlnArgAspValSerGlnArgSerIleTyrlSerGlnThrGlu (SEQ.ID.NO.: 49),
GlyGluAsnGlyValGlnLysAspValSerGlnLysSerIleTyrlSerGlnThrGlu (SEQ.ID.NO.: 50),
GlyGluAsnGlyValGlnLysAspLeuSerGlnThrSerIleTyrlSerGlnThrGlu (SEQ.ID.NO.: 51),
GlyGluAsnGlyValGlnLysAspValSerGlnSerSerIlePhelSerGlnThrGlu (SEQ.ID.NO.: 52),
GlyGluAsnGlyValGlnLysAspMetSerGlnSerSerIleTyrlThrGlnThrGlu (SEQ.ID.NO.: 53),
GlyGluAsnGlyValGlnLysAspValSerGlnArgSerIleTyrlThrGlnThrGlu (SEQ.ID.NO.: 54),
GlyGluAsnGlyValGlnLysAspValSerGlnSerSerIleTyrlSerGlnSerGlu (SEQ.ID.NO.: 55),
GlyGluAsnGlyValGlnLysAspValSerGlnArgSerIleTyrlSerAsnThrGlu (SEQ.ID.NO.: 56),
GlyLysAlaIleSerSerGlnTyrlSerAsnThrGluGluArgLeu (SEQ.ID.NO.: 57),
GlyArgGlyIleSerSerGlnTyrlSerAsnThrGluGluArgLeu (SEQ.ID.NO.: 59),
GlyLysGlyIleThrSerGlnTyrlSerAsnThrGluGluArgLeu (SEQ.ID.NO.: 60),
GlyLysGlyIleSerThrGlnTyrlSerAsnThrGluGluArgLeu (SEQ.ID.NO.: 61),
GlyLysGlyIleSerSerAsnTyrlSerAsnThrGluGluArgLeu (SEQ.ID.NO.: 62),

AlaLysGlyIleSerSerGlnTyrISerAsnThrGluGluArgLeu (SEQ.ID.NO.: 63),
GlyLysGlyIleSerSerGlnPheISerAsnThrGluGluArgLeu (SEQ.ID.NO.: 64),
GlyLysGlyIleSerSerGlnTyrIThrAsnThrGluGluArgLeu (SEQ.ID.NO.: 65),
GlyLysGlyIleSerSerGlnTyrISerAsnSerGluGluArgLeu (SEQ.ID.NO.: 58), and
GlyLysGlyIleSerSerGlnTyrISerAsnThrAspGluArgLeu (SEQ.ID.NO.: 46);
and the like.

The inclusion of the symbol "I" within an amino acid sequence indicates the point within that sequence where the oligopeptide is proteolytically cleaved by free PSA.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. Unless otherwise specified, named amino acids are understood to have the natural "L" stereoconfiguration

The following abbreviations are utilized in the specification and figures to denote the indicated amino acids and moieties:

hR or hArg:	homoarginine
hY or hTyr:	homotyrosine
Cha:	cyclohexylalanine
Amf:	4-aminomethylphenylalanine
DPL:	2-(4,6-dimethylpyrimidinyl)lysine
(imidazolyl)K:	N'-(2-imidazolyl)lysine
Me_2PO_3-Y:	O-dimethylphosphotyrosine
O-Me-Y:	O-methyltyrosine
TIC:	tetrahydro-3-isoquinoline carboxylic acid
MeL:	2-keto-3-amino-5-methylhexane
DAP:	1,3-diaminopropane

TFA:	trifluoroacetic acid
AA:	acetic acid

The method of treatment of the instant invention utilizes pharmaceutical compositions whose pharmaceutical activity is specific for cells that secrete enzymatically active PSA. Such compositions comprise the oligopeptides described herein above covalently bonded directly, or through a linker unit, to a pharmaceutical agent. Such a combination of an oligopeptide and pharmaceutical agent may be termed a conjugate. The pharmaceutical agent component of the conjugate may be selected from known compounds useful for treating conditions of the prostate, whose site of biological activity or the desired target of the biological activity is within the prostate or in close proximity to the prostate. Such pharmaceutical agents include, but are not limited to cytotoxic agents.

In a preferred embodiment, the method of treatment of the instant invention utilizes cytotoxic compositions whose cytotoxicity is specific for cells that secrete enzymatically active PSA. Such compositions comprise the oligopeptides, described herein above, covalently bonded directly, or through a linker unit, to a cytotoxic agent. Ideally, the cytotoxic activity of the cytotoxic agent is greatly reduced or absent when the oligopeptide containing the PSA proteolytic cleavage site is bonded directly, or through a chemical linker, to the cytotoxic agent and is intact. Also ideally, the cytotoxic activity of the cytotoxic agent increases significantly or returns to the activity of the unmodified cytotoxic agent upon proteolytic cleavage of the attached oligopeptide at the cleavage site. While it is not necessary for practicing this aspect of the invention, a preferred embodiment of this aspect of the invention is a conjugate wherein the oligopeptide, and the linker unit if present, are detached from the cytotoxic agent by the proteolytic activity of the free PSA and any other native proteolytic enzymes present in the tissue proximity, thereby releasing unmodified cytotoxic agent into the

physiological environment at the place of proteolytic cleavage. Pharmaceutically acceptable salts of the conjugates are also included.

It is understood that the oligopeptide of the instant invention that is conjugated to the cytotoxic agent, whether through a direct covalent bond or through a linker unit, does not need to be the oligopeptide that has the greatest recognition by free PSA and is most readily proteolytically cleaved by free PSA. Thus, the oligopeptide that is selected for incorporation in such an anti-BPH composition will be chosen both for its selective, proteolytic cleavage by free PSA and for the cytotoxic activity of the cytotoxic agent-proteolytic residue conjugate (or, in what is felt to be an ideal situation, the unmodified cytotoxic agent) which results from such a cleavage.

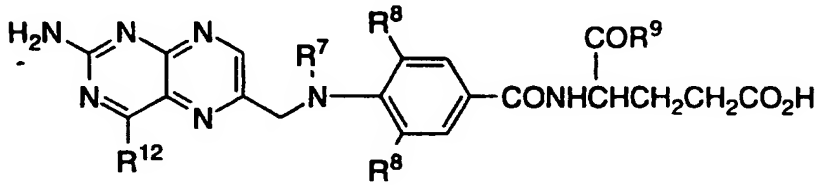
Because the conjugates utilized in the instant invention can be used for modifying a given biological response, cytotoxic agent is not to be construed as limited to classical chemical therapeutic agents. For example, the cytotoxic agent may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, α-interferon, β-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

The preferred cytotoxic agents include, in general, alkylating agents, antiproliferative agents, tubulin binding agents and the like. Preferred classes of cytotoxic agents include, for example, the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the cytotoxic nucleosides, the pteridine family of drugs, diynenes, the taxanes and the podophyllotoxins. Particularly useful members of those classes include, for example, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloro-methotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-

mercaptopurine, cytosine arabinoside, podophyllotoxin, or podophyllotoxin derivatives such as etoposide or etoposide phosphate, melphalan, vinblastine, vincristine, leurosidine, vindesine, leurosine, taxol and the like. Other useful cytotoxic agents include estramustine, cisplatin and cyclophosphamide. One skilled in the art may make chemical modifications to the desired cytotoxic agent in order to make reactions of that compound more convenient for purposes of preparing conjugates of the invention.

A highly preferred group of cytotoxic agents for the present invention include drugs of the following formulae:

THE METHOTREXATE GROUP OF FORMULA(1):

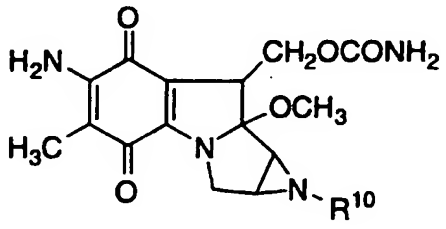


(1)

in which

R^{12} is	amino or hydroxy;
R^7 is	hydrogen or methyl;
R^8 is	hydrogen, fluoro, chloro, bromo or iodo;
R^9 is	hydroxy or a moiety which completes a salt of the carboxylic acid;

THE MITOMYCIN GROUP OF FORMULA (2):

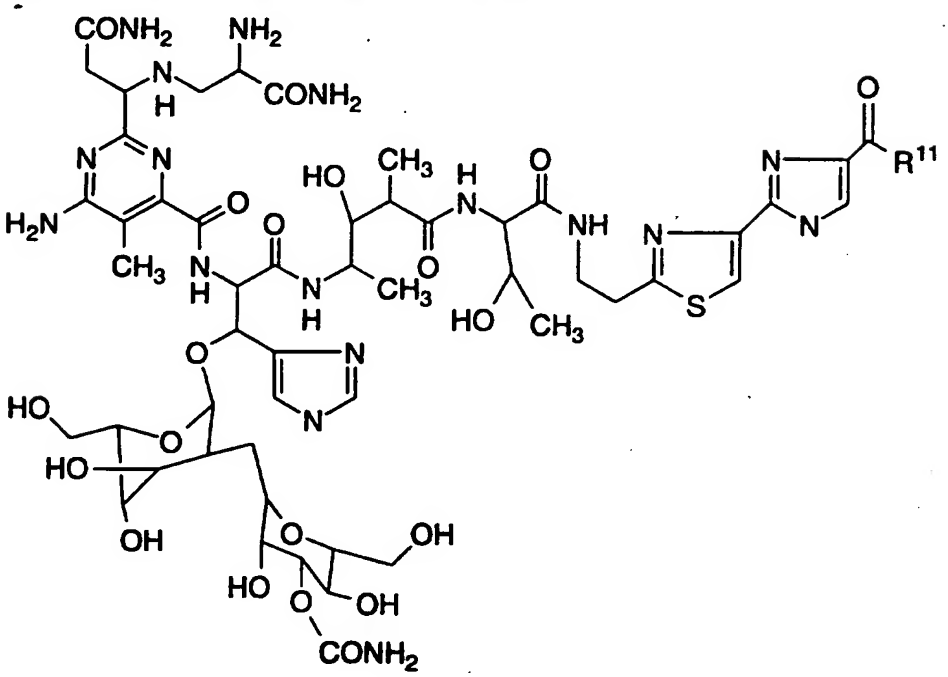


(2)

in which

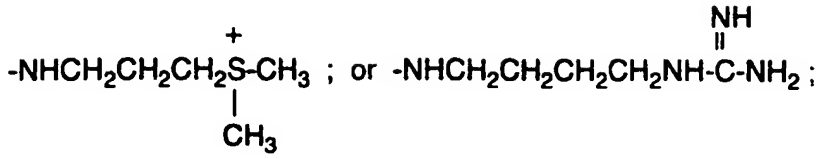
R^{10} is hydrogen or methyl;

THE BLEOMYCIN GROUP OF FORMULA (3)

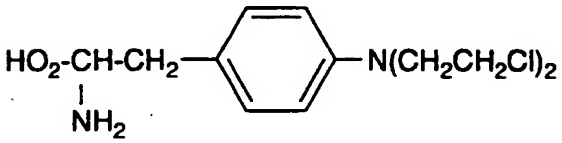


(3)

in which R^{11} is hydroxy, amino, C_1-C_3 alkylamino, di(C_1-C_3 alkyl)amino, C_4-C_6 polymethylene amino,

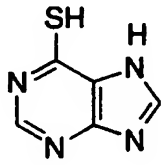


MELPHALAN OF FORMULA (4):



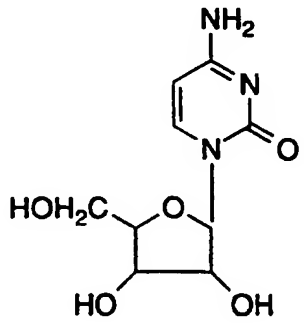
(4)

6-MERCAPTOPURINE OF FORMULA (5):



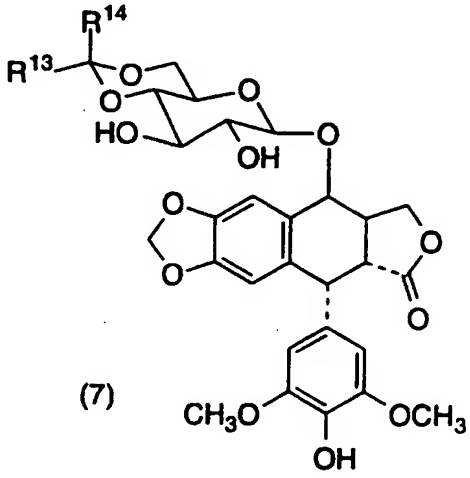
(5)

A CYTOSINE ARABINOSIDE OF FORMULA (6):



(6)

THE PODOPHYLLOTOXINS OF FORMULA(7):



(7)

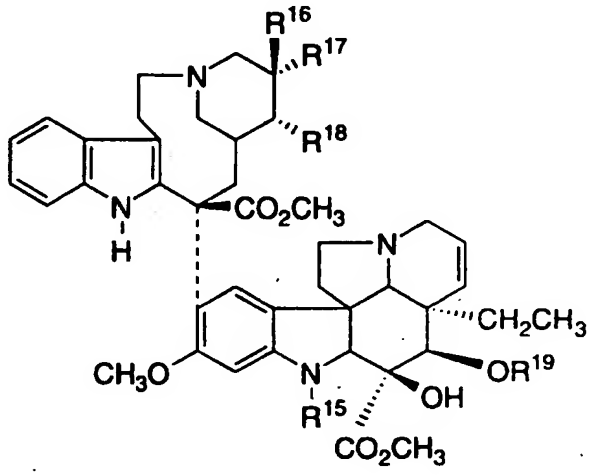
in which

R^{13} is hydrogen or methyl;

R^{14} is methyl or thienyl;

or a phosphate salt thereof;

THE VINCA ALKALOID GROUP OF DRUGS OF FORMULA (8):



(8)

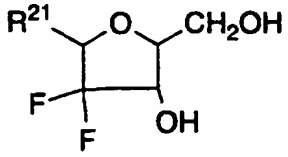
in which

R^{15} is H, CH_3 or CHO; when R^{17} and R^{18} are taken singly;

R^{18} is H, and one of R^{16} and R^{17} is ethyl and the other is H or OH; when R^{17} and R^{18} are taken together with the carbons to which they are attached, they form an oxirane ring in which case R^{16} is ethyl;

R^{19} is hydrogen, (C_1-C_3 alkyl)-CO, or chlorosubstituted (C_1-C_3 alkyl)-CO;

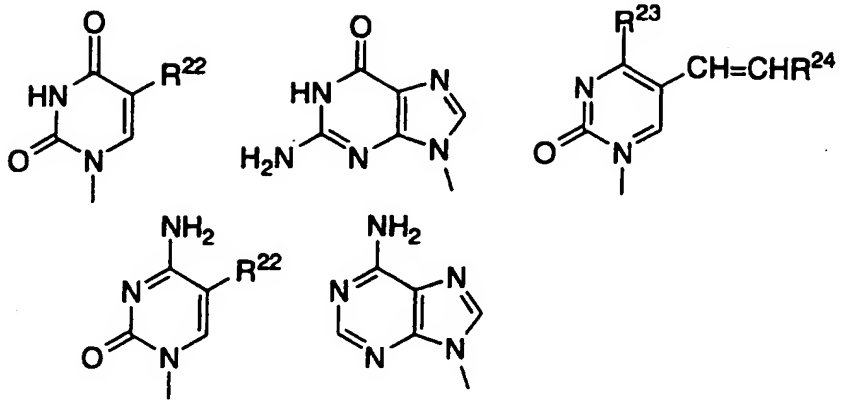
DIFLUORONUCLEOSIDES OF FORMULA (9):



(9)

in which

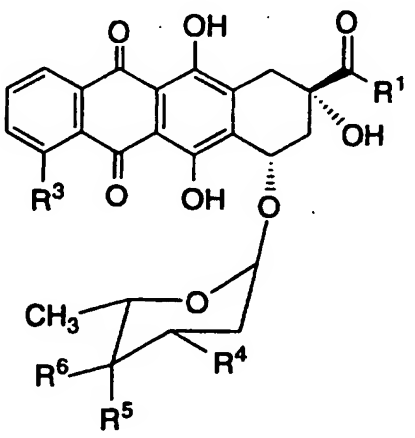
R^{21} is a base of one of the formulae:



in which

R^{22} is hydrogen, methyl, bromo, fluoro, chloro or iodo;
R^{23} is -OH or $-NH_2$;
R^{24} is hydrogen, bromo, chloro or iodo;
or,

THE ANTHRACYCLINES ANTIBIOTICS OF FORMULA (10):



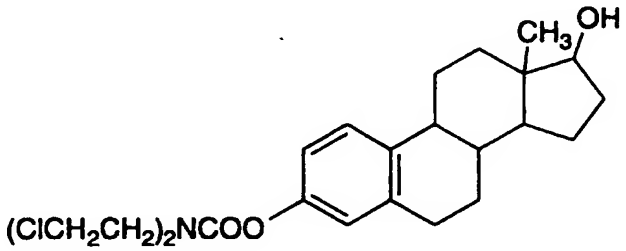
(10)

wherein

R^1 is -CH_3, -CH_2OH, -$CH_2OCO(CH_2)_3CH_3$, or -$CH_2OCOCH(OC_2H_5)_2$;

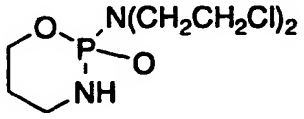
R^3 is -OCH_3, -OH or -H;
R^4 is -NH_2, -$NHCOCF_3$, 4-morpholinyl, 3-cyano-4-morpholinyl, 1-piperidinyl, 4-methoxy-1-piperidinyl, benzylamine, dibenzylamine, cyanomethylamine, or 1-cyano-2-methoxyethyl amine;
R5 is -OH -OTHP or -H; and
R^6 is -OH or -H provided that
R^6 is not -OH when R^5 is -OH or -OTHP.

ESTRAMUSTINE (11)



(11)

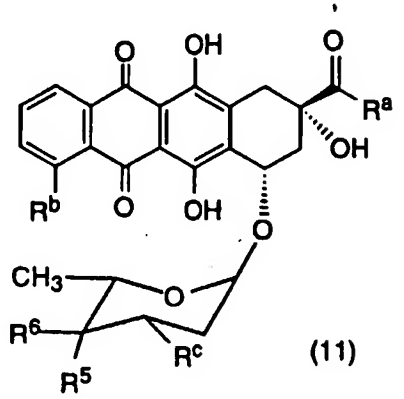
CYCLOPHOSPHAMIDE (12)



12

The most highly preferred drugs are the anthracycline antiobiotic agents of Formula (10), described previously. One skilled in the art understands that this structural formula includes compounds which are drugs, or are derivatives of drugs, which have acquired in the art different generic or trivial names. Table 1, which follows, represents a number of anthracycline drugs and their generic or trivial names and which are especially preferred for use in the present invention.

Table 1



(11)

Compound	R^a	R^b	R^c	R_5	R_6
daunorubicin[a]	CH_3	OCH_3	NH_2	OH	H
doxorubicin[b]	CH_2OH	OCH_3	NH_2	OH	H
detorubicin	$CH_2OCOCH(OC_2H_5)2$	OCH_3	NH_2	OH	H
carminomycin	CH_3	OH	NH_2	OH	H
idarubicin	CH_3	H	NH_2	OH	H
epirubicin	CH_2OH	OCH_3	NH_2	OH	OH
esorubicin	CH_2OH	OCH_3	NH_2	H	H
THP	CH_2OH	OCH_3	NH_2	OTHP	H
AD-32	$CH_2OCO(CH_2)3CH_3$	OCH_3	$NHCOCF_3$	OH	H

[a]"daunomycin" is an alternative name for daunorubicin
[b]"adriamycin" is an alternative name for doxorubicin

Of the compounds shown in Table 1, the most highly preferred cytotoxic agents are doxorubicin, vinblastine and desacetylvinblastine. Doxorubicin (also referred to herein as "DOX") is that anthracycline of Formula (10) in which R_1 is $-CH_2OH$, R_3 is $-OCH_3$, R_4 is $-NH_2$, R_5 is -OH, and R_6 is -H.

The oligopeptides, peptide subunits and peptide derivatives (also termed "peptides") incorporated in the conjugates utilized in the method of treatment of the present invention can be synthesized from their constituent amino acids by conventional peptide synthesis techniques, preferably by solid-phase technology. The peptides are then purified by reverse-phase high performance liquid chromatography (HPLC).

Standard methods of peptide synthesis are disclosed, for example, in the following works: Schroeder *et al.*, "The Peptides", Vol. I, Academic Press 1965; Bodansky *et al.*, "Peptide Synthesis", Interscience Publishers, 1966; McOmie (ed.) "Protective Groups in Organic Chemistry", Plenum Press, 1973; Barany *et al.*, "The Peptides: Analysis, Synthesis, Biology" 2, Chapter 1, Academic Press, 1980, and Stewart *et al.*, *"Solid Phase Peptide Synthesis"*, Second Edition, Pierce Chemical Company, 1984. The teachings of these works are hereby incorporated by reference.

The pharmaceutically acceptable salts of the compounds incorporated in the conjugates utilized in the method of treatment of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenyl-acetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric,

toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The conjugates utilized in the method of treatment of the instant invention which comprise the oligopeptide containing the PSA cleavage site and a cytotoxic agent may similarly be synthesized by techniques well known in the medicinal chemistry art. For example, a free amine moiety on the cytotoxic agent may be covalently attached to the oligopeptide at the carboxyl terminus such that an amide bond is formed. Similarly, an amide bond may be formed by covalently coupling an amine moiety of the oligopeptide and a carboxyl moiety of the cytotoxic agent. For these purposes a reagent such as 2-(1H-benzotriazol-1-yl)-1,3,3-tetramethyluronium hexafluorophosphate (known as HBTU) and 1-hyroxybenzotriazole hydrate (known as HOBT), dicyclohexyl- carbodiimide (DCC), N-ethyl-N-(3-dimethylaminopropyl)- carbodiimide (EDC), diphenylphosphorylazide (DPPA), benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP) and the like, used in combination or singularly, may be utilized.

Furthermore, the instant conjugate may be formed by a non-peptidyl bond between the PSA cleavage site and a cytotoxic agent. For example, the cytotoxic agent may be covalently attached to the carboxyl terminus of the oligopeptide via a hydroxyl moiety on the cytotoxic agent, thereby forming an ester linkage. For this purpose a reagent such as a combination of HBTU and HOBT, a combination of BOP and imidazole, a combination of DCC and DMAP, and the like may be utilized. The carboxylic acid may also be activated by forming the nitro-phenyl ester or the like and reacted in the presence of DBU (1,8-diazabicyclo[5,4,0]undec-7-ene.

The instant conjugate may also be formed by attachment of the oligopeptide to the cytotoxic agent via a linker unit. Such linker units include, for example, a biscarbonyl alkyl diradical whereby an amine moiety on the cytotoxic agent is connected with the linker unit to form an amide bond and the amino terminus of the oligopeptide is connected with the other end of the linker unit also forming an amide bond. Conversely,

a diaminoalkyl diradical linker unit, whereby a carbonyl moiety on the cyctotoxic agent is covalently attacted to one of the amines of the linker unit while the other amine of the linker unit is covalently attached to the C terminus of the oligopeptide, may also be uselful. Other such linker units which are stable to the physiological environment when not in the presence of free PSA, but are cleavable upon the cleavage of the PSA proteolytic cleavage site, are also envisioned. Furthermore, linker units may be utilized that, upon cleavage of the PSA proteolytic cleavage site, remain attached to the cytotoxic agent but do not significantly decrease the cytotoxic activity of such a post-cleavage cytotoxic agent derivative when compared with an unmodified cytotoxic agent.

One skilled in the art understands that in the synthesis of conjugates utilized in the method of treatment of the invention, one may need to protect or block various reactive functionalities on the starting compounds and intermediates while a desired reaction is carried out on other portions of the molecule. After the desired reactions are complete, or at any desired time, normally such protecting groups will be removed by, for example, hydrolytic or hydrogenolytic means. Such protection and deprotection steps are conventional in organic chemistry. One skilled in the art is referred to Protective Groups in Organic Chemistry, McOmie, ed., Plenum Press, NY, NY (1973); and, Protective Groups in Organic Synthesis, Greene, ed., John Wiley & Sons, NY, NY (1981) for the teaching of protective groups which may be useful in the preparation of compounds of the present invention.

By way of example only, useful amino-protecting groups may include, for example, C_1-C_{10} alkanoyl groups such as formyl, acetyl, dichloroacetyl, propionyl, hexanoyl, 3,3-diethylhexanoyl, γ-chlorobutryl, and the like; C_1-C_{10} alkoxycarbonyl and C_5-C_{15} aryloxycarbonyl groups such as tert-butoxycarbonyl, benzyloxycarbonyl, allyloxycarbonyl, 4-nitrobenzyloxycarbonyl, fluorenylmethyloxycarbonyl and cinnamoyloxycarbonyl; halo-(C_1-C_{10})-alkoxycarbonyl such as 2,2,2-trichloroethoxycarbonyl; and C_1-C_{15} arylalkyl and alkenyl group such as benzyl, phenethyl, allyl, trityl, and the like. Other commonly

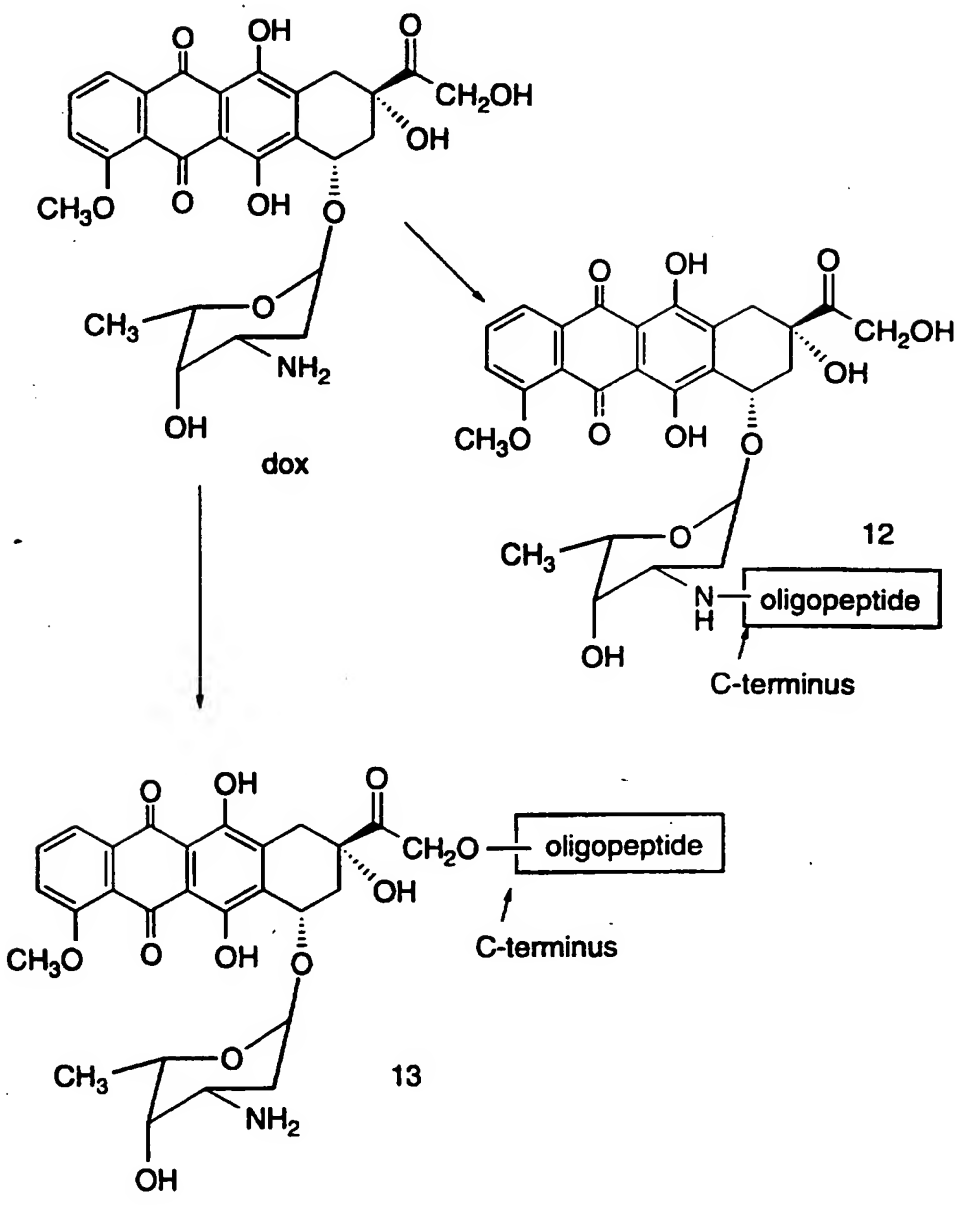
used amino-protecting groups are those in the form of enamines prepared with β-keto-esters such as methyl or ethyl acetoacetate.

Useful carboxy-protecting groups may include, for example, C_1-C_{10} alkyl groups such as methyl, tert-butyl, decyl; halo-C_1-C_{10} alkyl such as 2,2,2-trichloroethyl, and 2-iodoethyl; C_5-C_{15} arylalkyl such as benzyl, 4-methoxybenzyl, 4-nitrobenzyl, triphenylmethyl, diphenylmethyl; C_1-C_{10} alkanoyloxymethyl such as acetoxymethyl, propionoxymethyl and the like; and groups such as phenacyl, 4-halophenacyl, allyl, dimethylallyl, tri-(C_1-C_3 alkyl)silyl, such as trimethylsilyl, β-p-toluenesulfonylethyl, β-p-nitrophenyl-thioethyl, 2,4,6-trimethylbenzyl, β-methylthioethyl, phthalimidomethyl, 2,4-dinitrophenylsulphenyl, 2-nitrobenzhydryl and related groups.

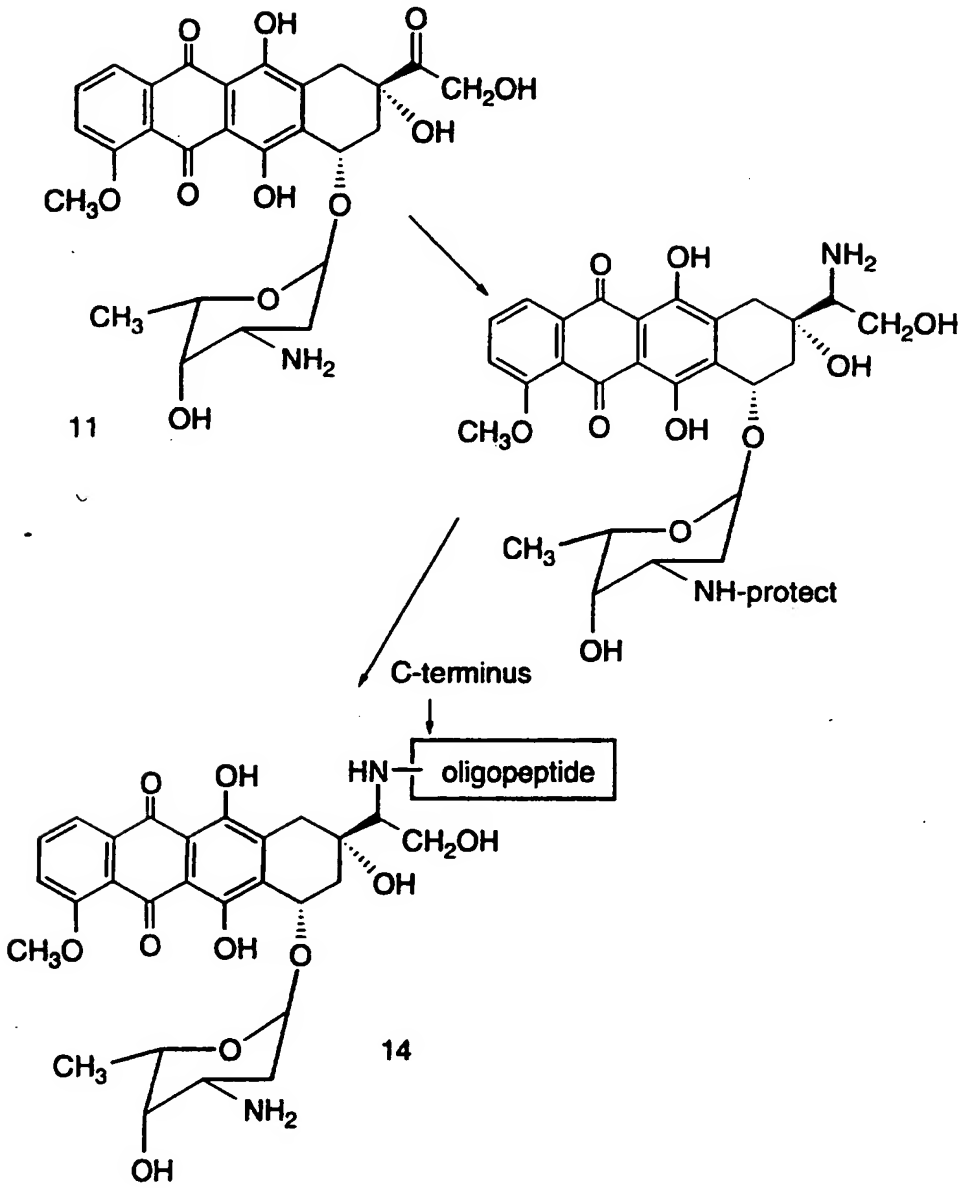
Similarly, useful hydroxy protecting groups may include, for example, the formyl group, the chloroacetyl group, the benzyl group, the benzhydryl group, the trityl group, the 4-nitrobenzyl group, the trimethylsilyl group, the phenacyl group, the tert-butyl group, the methoxymethyl group, the tetrahydropyranyl group, and the like.

With respect to the preferred embodiment of the instant method of treatment in which an oligopeptide is combined with the anthracycline antibiotic doxorubicin, the following Reaction Schemes illustrate the synthsis of the conjugates of the instant invention.

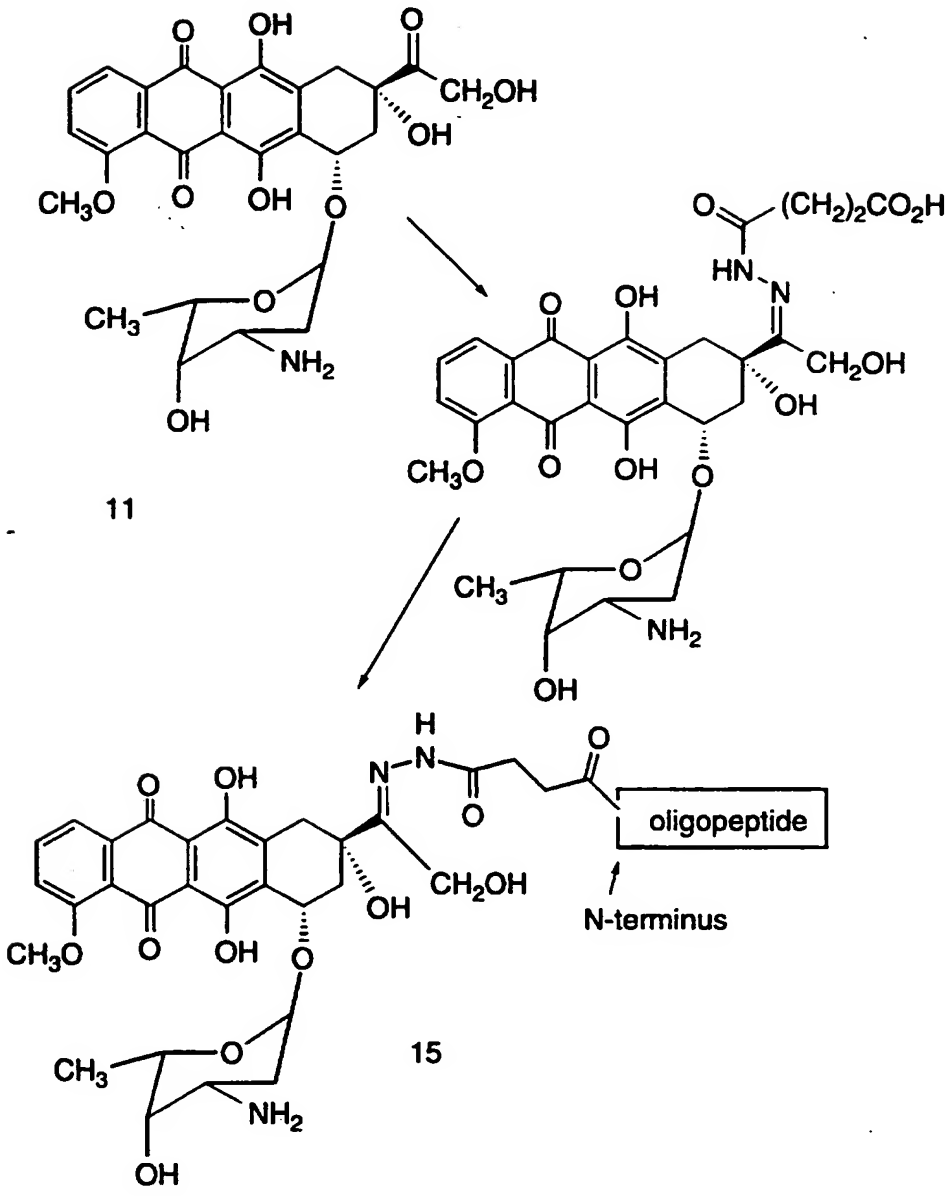
REACTION SCHEME I



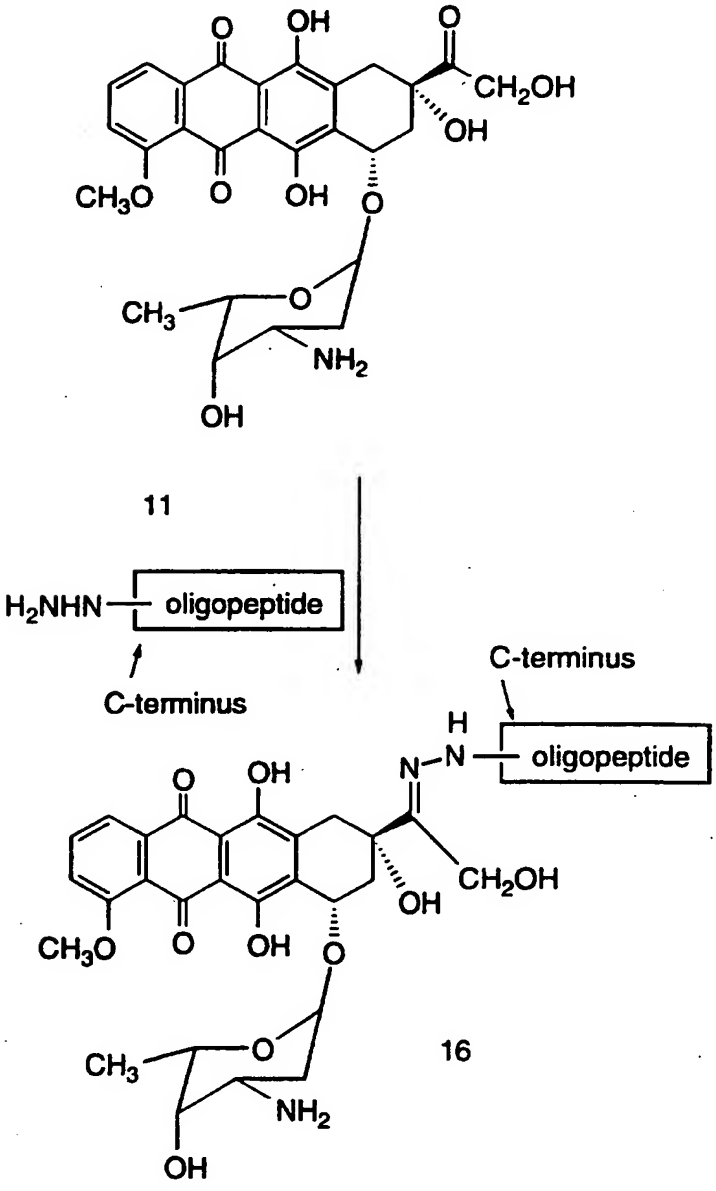
REACTION SCHEME II



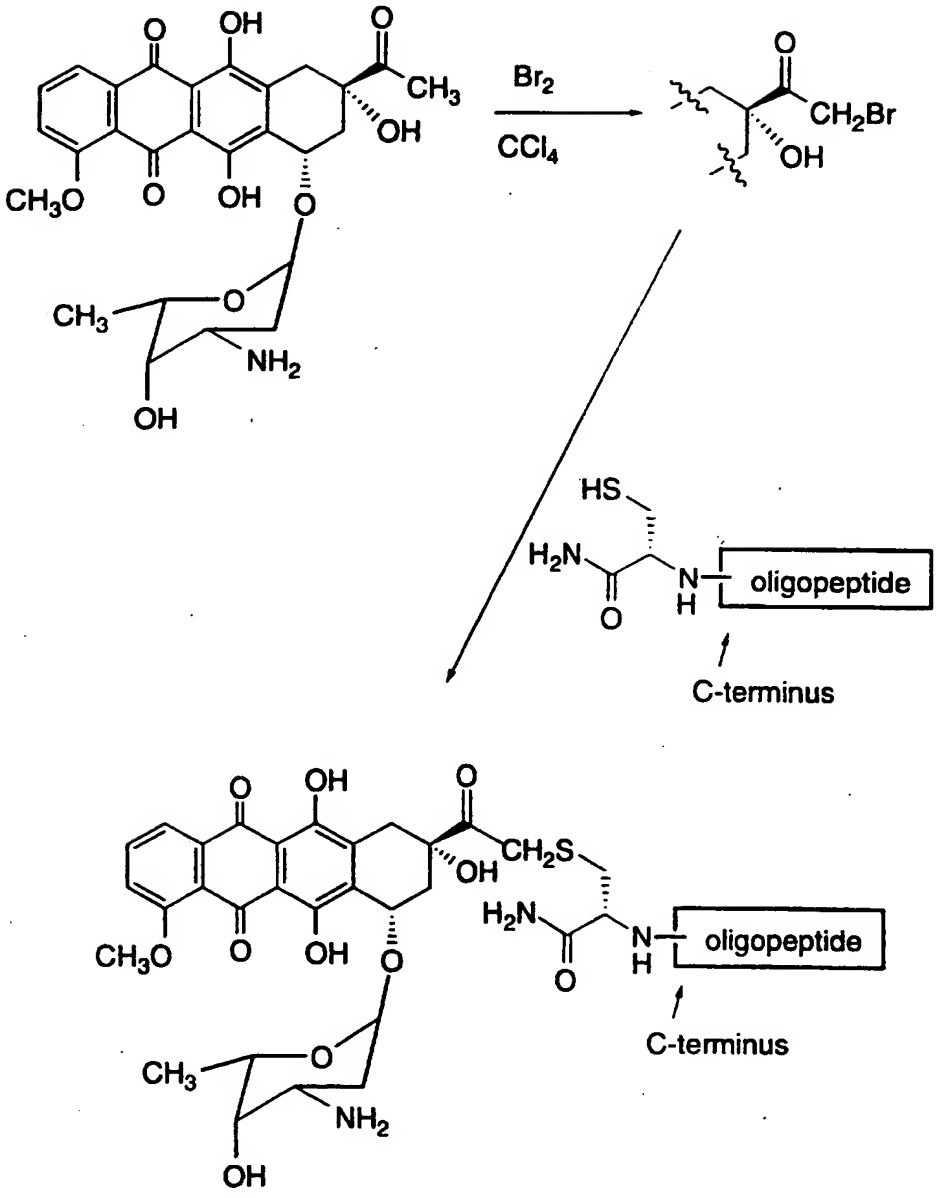
REACTION SCHEME III



REACTION SCHEME IV



REACTION SCHEME V

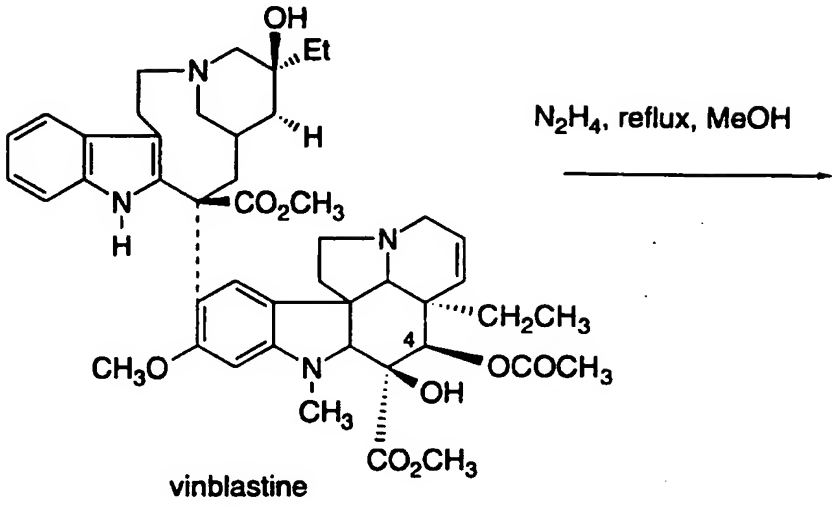


Reaction Scheme VI illustrates preparation of conjugates utilized in the instant method of treatment wherein the oligopeptides are combined with the vinca alkaloid cytotoxic agent vinblastine. Attachment of the N-terminus of the oligopeptide to vinblastine is illustrated (S.P. Kandukuri et al. J. Med. Chem. 28:1079-1088 (1985)).

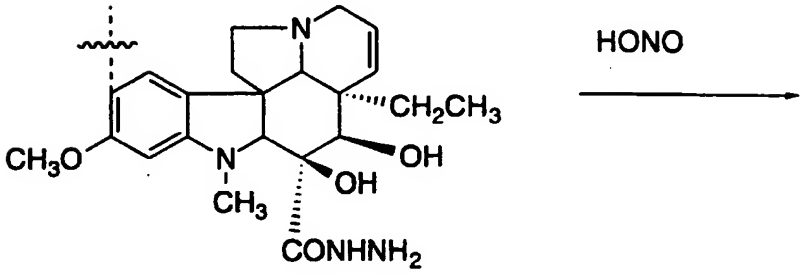
Reaction Scheme VII illustrates preparation of conjugates utilized in the instant method of treatment wherein the oligopeptides are combined with the vinca alkaloid cytotoxic agent vinblastine wherein the attachment of vinblastine is at the C-terminus of the oligopeptide. The use of the 1,3-diaminopropane linker is illustrative only; other spacer units between the carbonyl of vinblastine and the C-terminus of the oligopeptide are also envisioned. Furthermore, Scheme VII illustrates a synthesis of conjugates wherein the C-4-position hydroxy moiety is reacetylated following the addition of the linker unit. Applicants have discovered that the desacetyl vinblastine conjugate is also efficacious and may be prepared by eliminating the steps shown in Reaction Scheme VII of protecting the primary amine of the linker and reacting the intermediate with acetic anhydride, followed by deprotection of the amine. Conjugation of the oligopeptide at other positions and functional groups of vinblastine may be readily accomplished by one of ordinary skill in the art and is also expected to provide compounds useful in the treatment of benign prostatic hyperplasia.

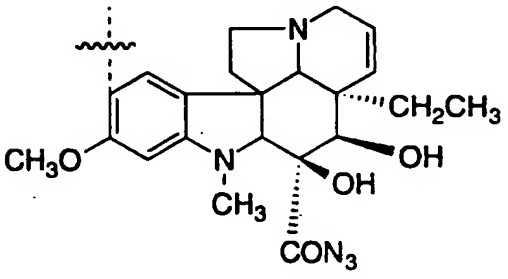
It is also understood that conjugates may be prepared wherein the N-terminus of the oligopeptide utilized in the instant method of treatment is combined with one cytotoxic agent, such as vinblastine, while the C-terminus is simultaneously attached to another cytotoxic agent, which is the same or different cytotoxic agent, such as doxorubicin. Reaction Scheme VIII illustrates the synthesis of such a polycytotoxic agent conjugate. Such a polycytotoxic conjugate may offer advantages over a conjugate containing only one cytotoxic agent.

REACTION SCHEME VI

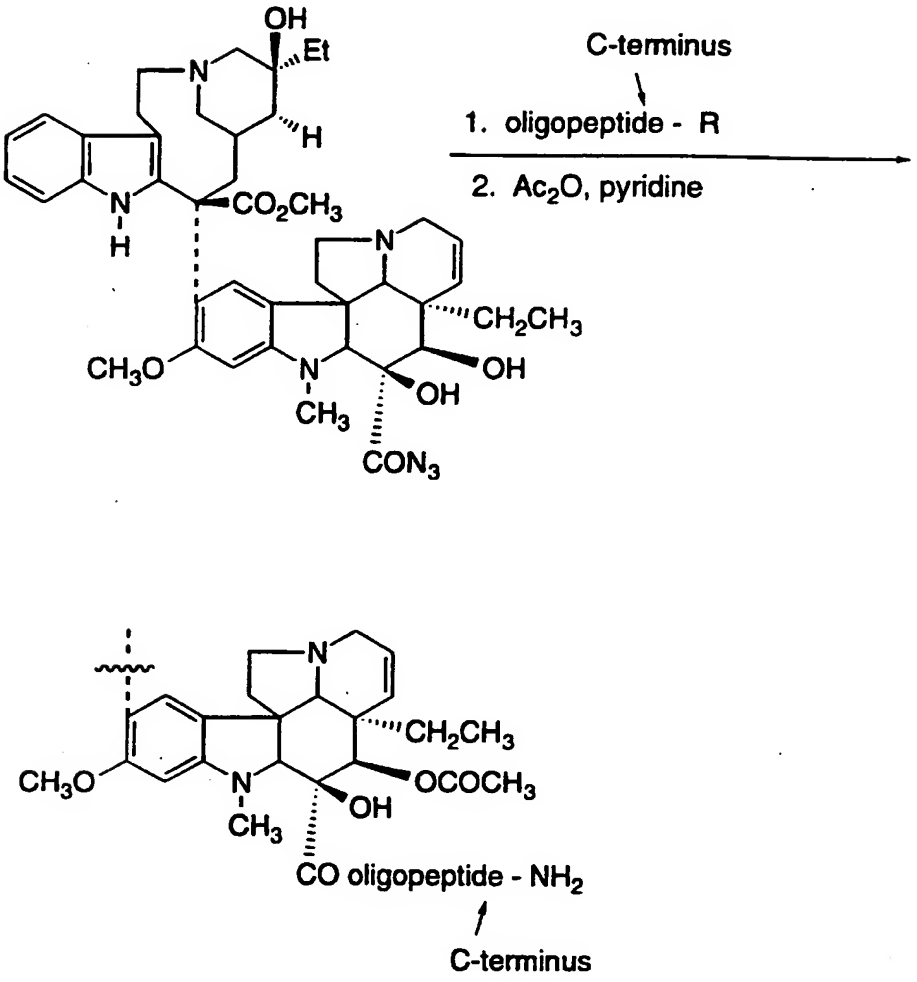


vinblastine



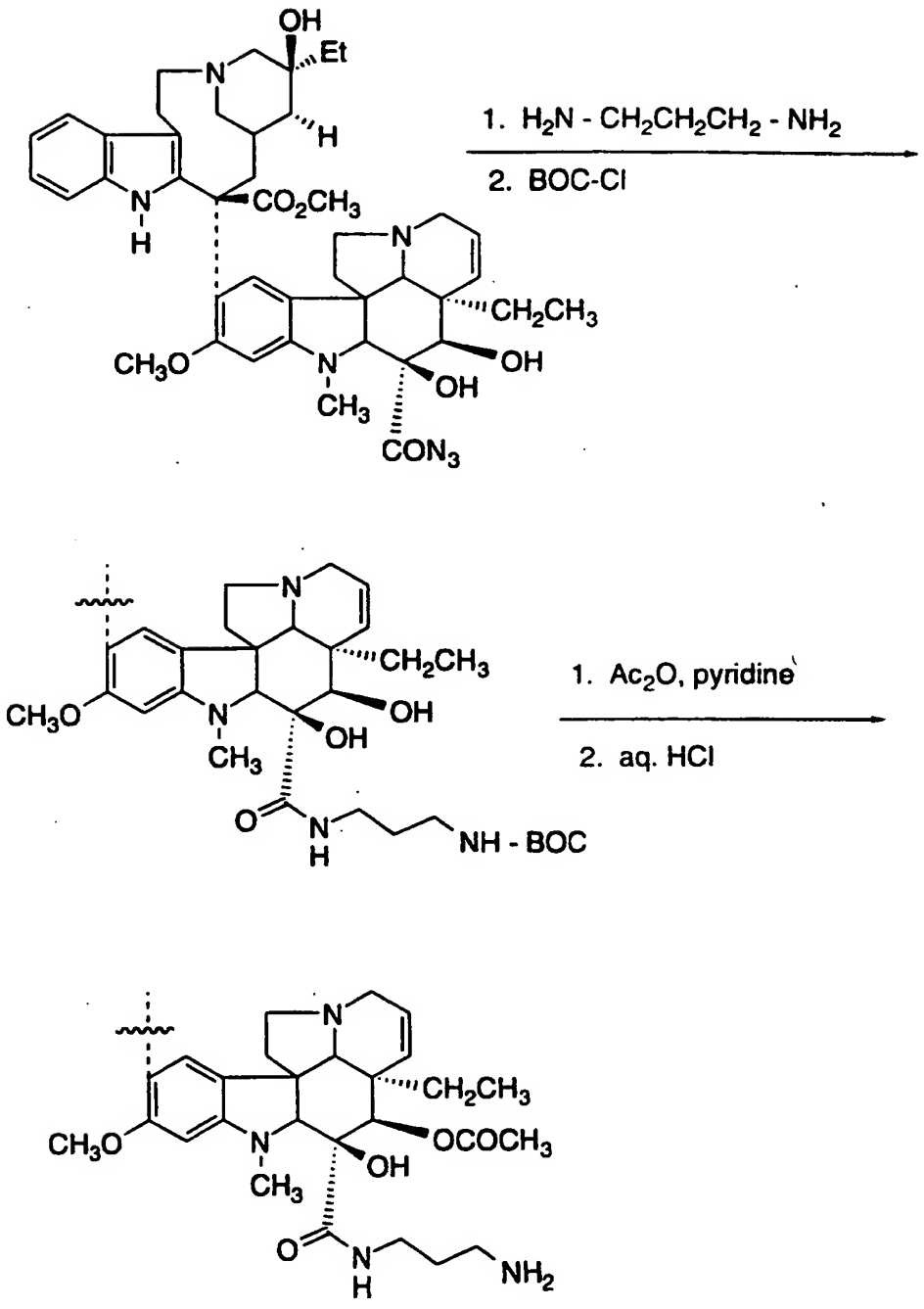


REACTION SCHEME VI (Continued)

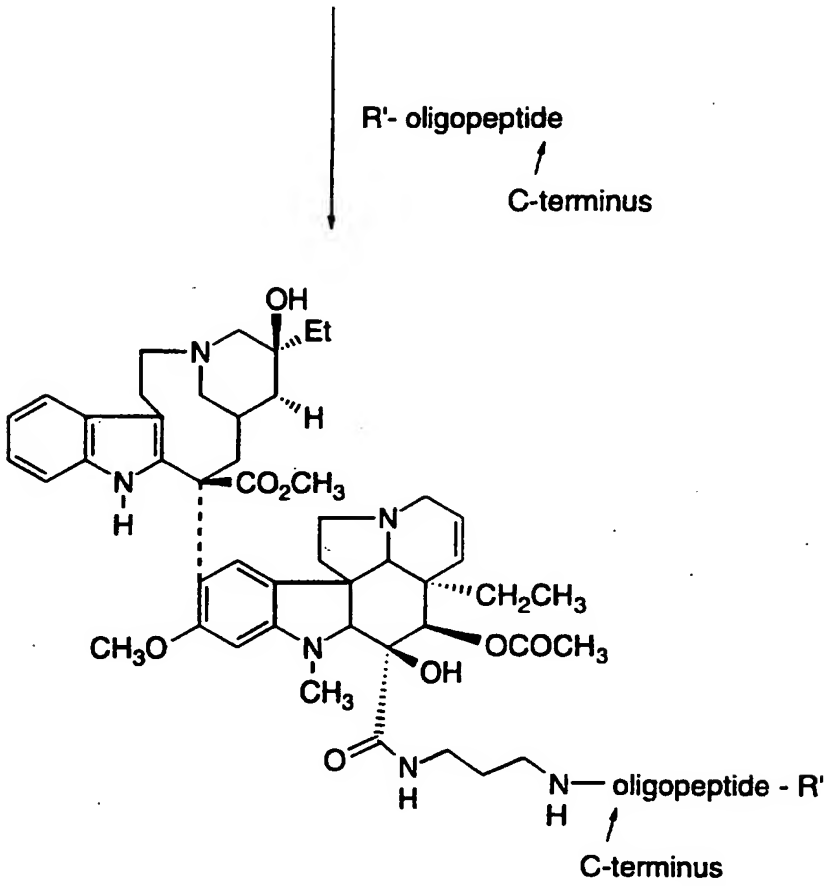


wherein R is -NH_2, -O-alkyl and the like

REACTION SCHEME VII



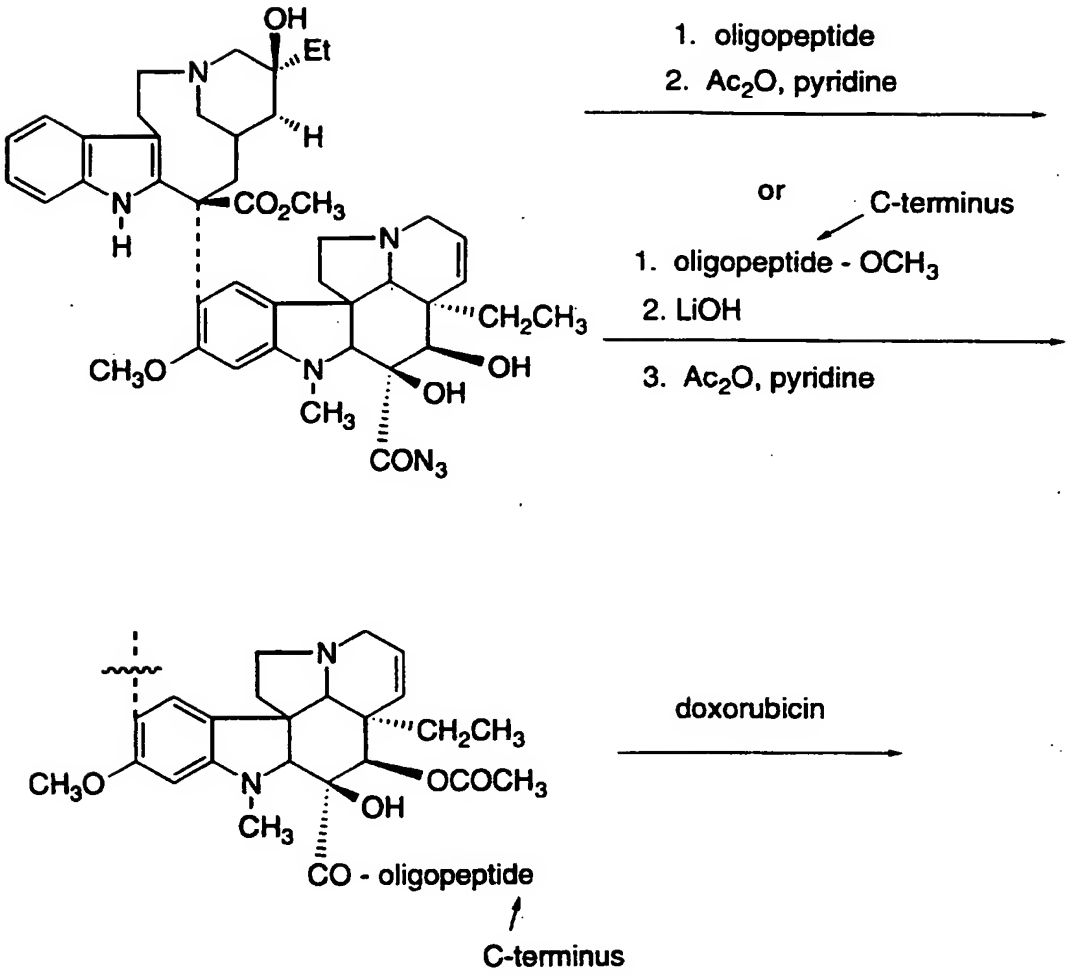
REACTION SCHEME VII (Continued)



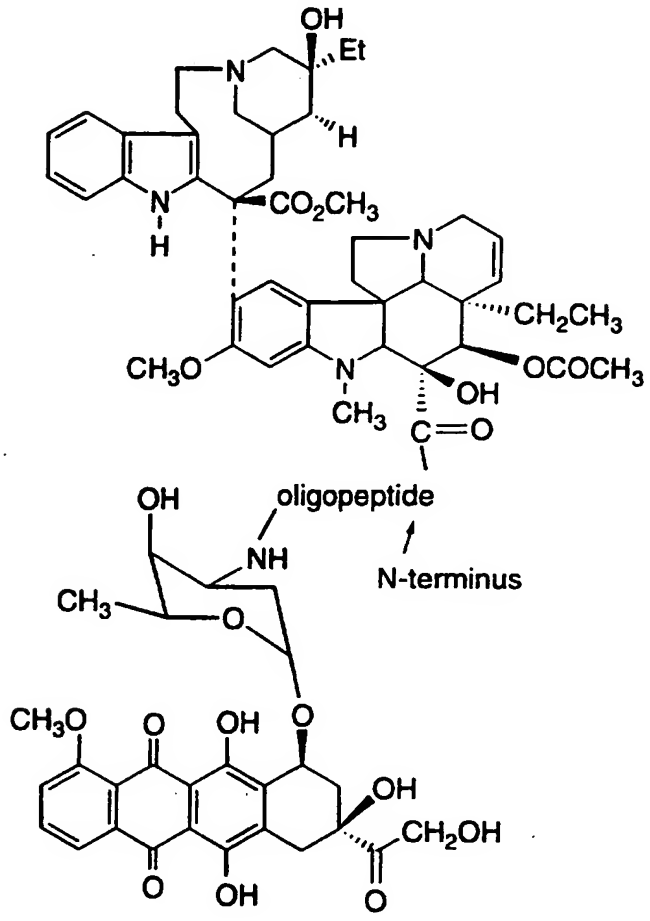
wherein R' is acetyl, alkyl, hydrogen or the like

5

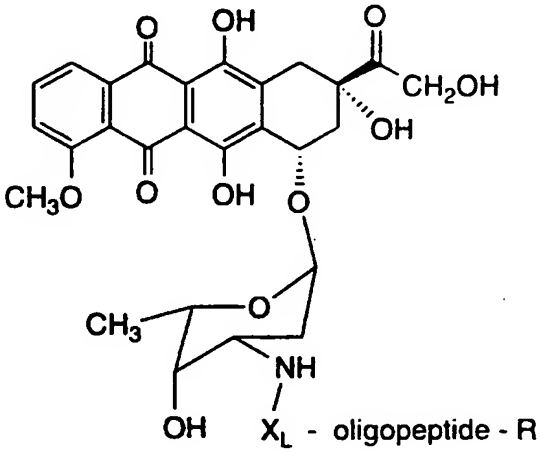
REACTION SCHEME VIII



REACTION SCHEME VIII (Continued)



The oligopeptide-cytotoxic agent conjugate utilized in the method of treatment of the instant invention wherein the cytotoxic agent is the preferred cytotoxic agent doxorubicin may be described by the general formula I below:



wherein:

oligopeptide is an oligopeptide which is specifically recognized by the free prostate specific antigen (PSA) and is capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen;

X_L is absent or is an amino acid selected from:

a) phenylalanine,
b) leucine,
c) valine,
d) isoleucine,
e) (2-naphthyl)alanine,
f) cyclohexylalanine,
g) diphenylalanine,
h) norvaline,
i) norleucine, and

j) 1,2,3,4-tetrahydroiso quinoline-3-carboxylic acid;

R is hydrogen or -(C=O)R^1; and

R^1 is C_1-C_6-alkyl or aryl,

or the pharmaceutically acceptable salt thereof.

In a preferred embodiment of the instant method of treatment of BPH:

oligopeptide is an oligomer that comprises an amino acid sequence selected from:

a) AsnLysIleSerTyrGlnlSer (SEQ.ID.NO.: 13),

b) LysIleSerTyrGlnlSer (SEQ.ID.NO.: 14),

c) GlyGluAsnGlyValGlnLysAspValSerGlnXaaSerIleTyrlSerGlnThrGlu (SEQ.ID.NO.: 15) ,

d) GlyLysGlyIleSerSerGlnTyrlSerAsnThrGluGluArgLeu (SEQ.ID.NO.: 2),

e) AsnLysIleSerTyrTyrlSer (SEQ.ID.NO.: 127),

f) AsnLysAlaSerTyrGlnlSer (SEQ.ID.NO.: 128),

g) SerTyrGlnlSerSer (SEQ.ID.NO.: 129),

h) LysTyrGlnlSerSer (SEQ.ID.NO.: 140);

i) hArgTyrGlnlSerSer (SEQ.ID.NO.: 141);

j) hArgChaGlnlSerSer (SEQ.ID.NO.: 185); and

k) TyrGlnlSerSer (SEQ.ID.NO.: 186);

wherein Xaa is any natural amino acid;

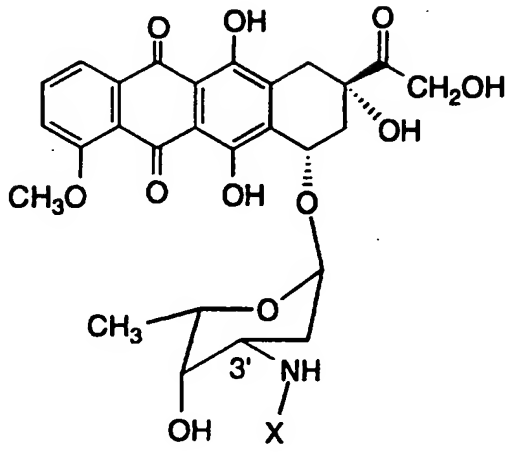
X_L is absent or is an amino acid selected from:

a) leucine,
b) isoleucine,
c) norleucine, and
d) valine; and

R is acetyl, pivaloyl or benzoyl,

or the pharmaceutically acceptable salt thereof.

The following compounds are specific examples of the oligopeptide-cytotoxic agent conjugate utilized in the method of treatment of the instant invention:



wherein X is:

AsnLysIleSerTyrGlnSer— (SEQ.ID.NO.: 13),

AsnLysIleSerTyrGlnSerSer— (SEQ.ID.NO.: 16),

AsnLysIleSerTyrGlnSerSerSer — (SEQ.ID.NO.:17),

AsnLysIleSerTyrGlnSerSerSerThr — (SEQ.ID.NO.:10),

AsnLysIleSerTyrGlnSerSerSerThrGlu — (SEQ.ID.NO.: 3),

AlaAsnLysIleSerTyrGlnSerSerSerThrGlu — (SEQ.ID.NO.: 11),

N-terminus

Ac—AlaAsnLysIleSerTyrGlnSerSerSerThr— (SEQ.ID.NO.: 117),

Ac—AlaAsnLysIleSerTyrGlnSerSerSerThrLeu— (SEQ.ID.NO.: 70),

Ac—AlaAsnLysAlaSerTyrGlnSerAlaSerThrLeu— (SEQ.ID.NO.: 118),

Ac—AlaAsnLysAlaSerTyrGlnSerAlaSerLeu— (SEQ.ID.NO.: 119),

Ac—AlaAsnLysAlaSerTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 120),

Ac—AlaAsnLysAlaSerTyrGlnSerSerLeu— (SEQ.ID.NO.: 121).

Ac—SerTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 144),

Ac—hArgTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 145).

Ac—LysTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 124), or (Compound 4)

Ac—LysTyrGlnSerSerNle— (SEQ.ID.NO.: 146).

N-terminus

or the pharmaceutically acceptable salt thereof.

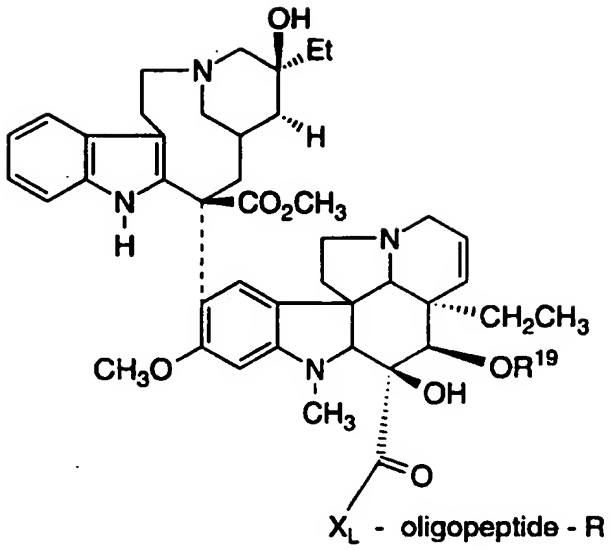
Further examples of conjugates of an oligopeptide and doxorubicin wherein the N-terminus of the oligopeptide is acylated and the C-terminus of the oligopeptide is attached to the doxorubicin at the 3'-amine are as follows:

Ac-hArgTyrGln-SerSerPro-dox(3') (SEQ.ID.NO.: 151)
Ac-hArgTyrGln-SerPro-dox(3') (SEQ.ID.NO.: 177)
Ac-hArgTyrGln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 154)

Ac-AmfTyrGln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 155)
H_2NCO-hArgTyrGln-SerSerSerLeu-dox(3') (SEQ.ID.NO.: 156)
Ac-LysTyrGln-SerSerNle-dox(3') (SEQ.ID.NO.: 146)
Ac-LysTyrGln-SerLysNle-dox(3') (SEQ.ID.NO.: 178)
Ac(cis-p-NH_2Cha)TyrGlnSerSerNledox(3') (SEQ.ID.NO.: 161)
Ac-AlaAspLysAla(hArg)TyrGln-SerSerLeu-dox(3') (SEQ.ID.NO.: 160)
Ac-hArgTyrGln-SerAsn-dox(3') (SEQ.ID.NO.: 153)
Ac-hArgTyrGln-SerSerHis-dox(3') (SEQ.ID.NO.: 152)
Ac-(imidazolyl)LysTyrGln-SerSerLeu-dox(3') (SEQ.ID.NO.: 159)
Ac-(imidazolyl)LysTyrGlnSerSerSerNle-dox(3') (SEQ.ID.NO.: 162)
Ac-hArg(Cha)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 163)
Ac-hArg(Me_2PO_3Tyr)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 167)
Ac-hArgTyrGln-SerSerSerhArg-dox(3') (SEQ.ID.NO.: 164)
Ac-hArg(3-Iodo-Tyr)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 166)
Ac-hArg(O-Me-Tyr)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 169)
Ac-hArg(p-NH_2-Phe)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 179)
Ac-hArg(Cha)Gln-SerSerNle-dox(3') (SEQ.ID.NO.: 174)
Ac-hArg(Cha)Gln-SerProNle-dox(3') (SEQ.ID.NO.: 175)
Ac(imidazolyl)Lys(Cha)GlnSerSerSerNle-dox(3') (SEQ.ID.NO.: 172)
Ac-hArg(7-HO-TIC)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 180)
Ac-hArg(3-Fluoro)TyrGlnSerSerSerNle-dox(3') (SEQ.ID.NO.: 176)
Ac-(ornithine)TyrGln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 181)
Ac-LysAlaAlaSerSerSerLeu-dox(3') (SEQ.ID.NO.: 183)
Ac-hArgh(Cha)Gln-SerSerNle-dox(3') (SEQ.ID.NO.: 149)
Ac-AlaArgLysAlaSerTyrGln-SerLeu-dox(3') (SEQ.ID.NO.: 193) and
Ac-(Orn)TyrGln-SerSerSerLeu-dox(3') (SEQ.ID.NO.: 194)

or the pharmaceutically acceptable salt thereof.

The oligopeptide-cytotoxic agent conjugate utilized in the method of treatment of the instant invention wherein the cytotoxic agent is the preferred cytotoxic agent vinblastine or desacetylvinblastine may be described by the general formula I below:



wherein:

oligopeptide is an oligopeptide which is specifically recognized by the free prostate specific antigen (PSA) and is capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen;

X_L is absent or is an amino acid selected from:

a) phenylalanine,
b) leucine,
c) valine,
d) isoleucine,
e) (2-naphthyl)alanine,
f) cyclohexylalanine,
g) diphenylalanine,
h) norvaline, and
i) norleucine, and
j) 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; or

X_L is - NH - $(CH_2)_n$ - NH -

R is hydrogen or -(C=O)R^1;

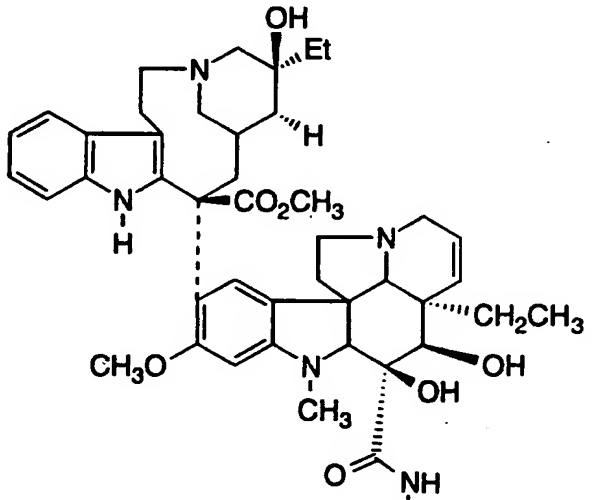
R^1 is C_1-C_6-alkyl or aryl;

R^{19} is hydrogen or acetyl; and

n is 1, 2, 3, 4 or 5,

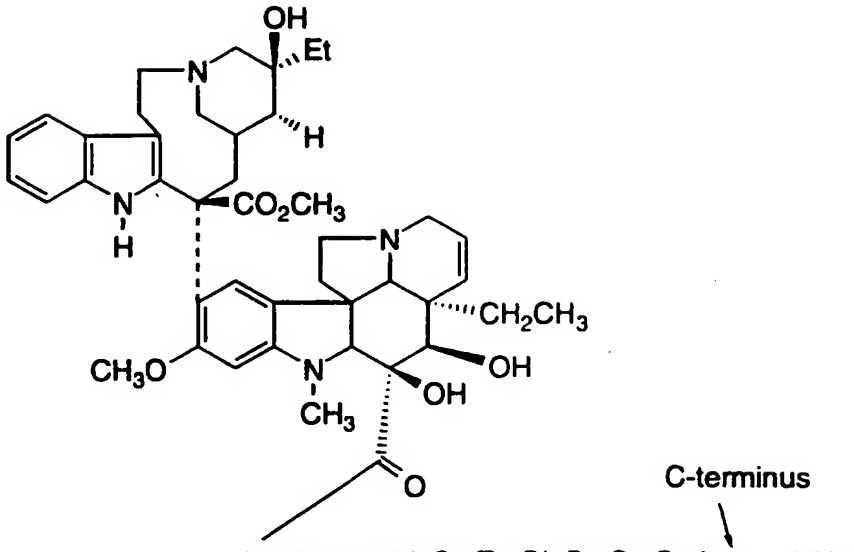
or the pharmaceutically acceptable salt thereof.

The following compounds are specific examples of the oligopeptide-desacetylvinblastine conjugate utilized in the method of treatment of the instant invention:



Compound 14

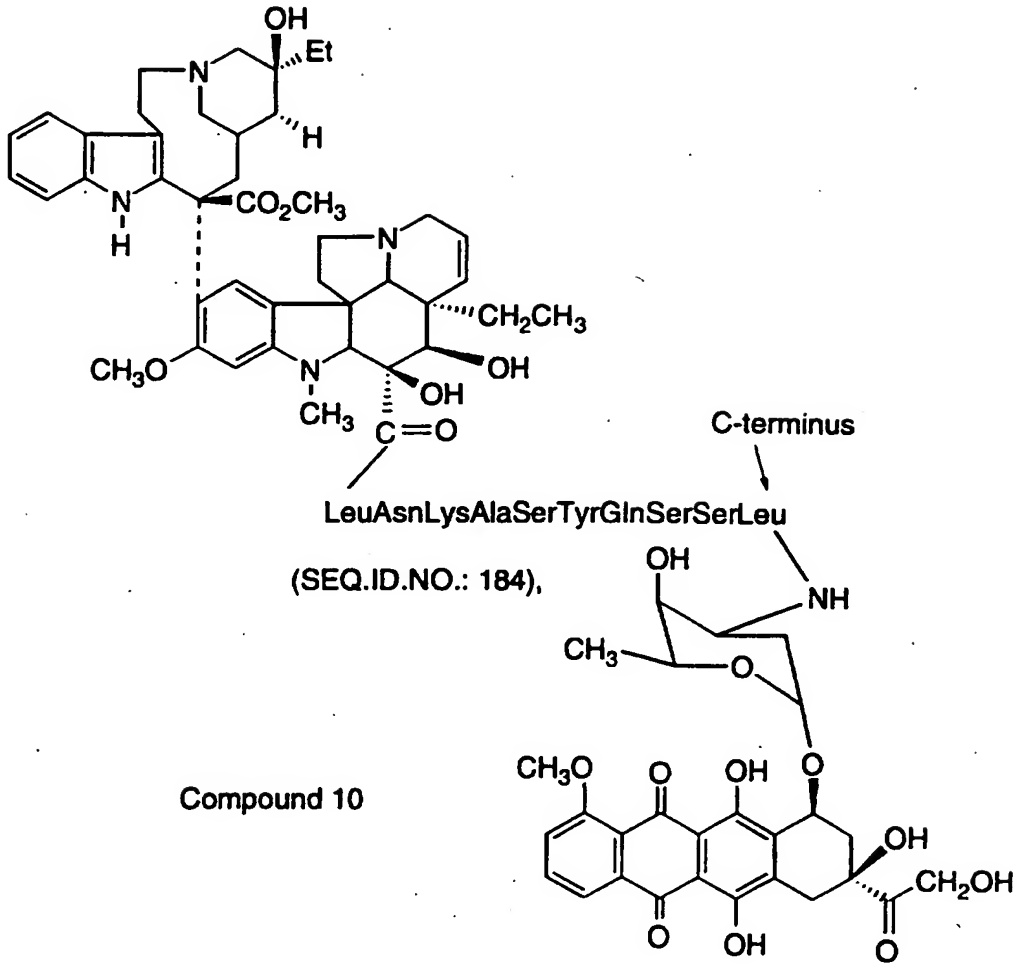
(SEQ.ID.NO.: 183),



Compound 5 (SEQ.ID.NO.: 184),

or the pharmaceutically acceptable salt thereof.

The following compounds is a specific example of the polycytotoxic agent conjugates utilized in the method of treatment of the instant invention:



Compound 10

or the pharmaceutically acceptable salt thereof.

It is well known in the art, and understood in the instant invention, that peptidyl therapeutic agents such as the oligopeptide-cytotoxic agent conjugates preferably have the terminal amino moiety of any oligopeptide substituent protected with a suitable protecting group, such as acetyl, benzoyl, pivaloyl and the like. Such protection of the terminal amino group reduces or eliminates the enzymatic degradation of such peptidyl therapeutic agents by the action of exogenous amino

peptidases which are present in the blood plasma of warm blooded animals.

The oligopeptide-cytotoxic agent conjugates utilized in the method of treatment of the instant invention are administered to the patient in the form of a pharmaceutical composition which comprises a conjugate of Formula (I) and a pharmaceutically acceptable carrier, excipient or diluent therefor. As used, "pharmaceutically acceptable" refers to those agents which are useful in the treatment or diagnosis of a warm-blooded animal including, for example, a human, equine, procine, bovine, murine, canine, feline, or other mammal, as well as an avian or other warm-blooded animal. The preferred mode of administration is parenterally, particularly by the intravenous, intramuscular, subcutaneous, intraperitoneal, or intralymphatic route. Such formulations can be prepared using carriers, diluents or excipients familiar to one skilled in the art. In this regard, See, e.g. Remington's Pharmaceutical Sciences, 16th ed., 1980, Mack Publishing Company, edited by Osol et al. Such compositions may include proteins, such as serum proteins, for example, human serum albumin, buffers or buffering substances such as phosphates, other salts, or electrolytes, and the like. Suitable diluents may include, for example, sterile water, isotonic saline, dilute aqueous dextrose, a polyhydric alcohol or mixtures of such alcohols, for example, glycerin, propylene glycol, polyethylene glycol and the like. The compositions may contain preservatives such as phenethyl alcohol, methyl and propyl parabens, thimerosal, and the like. If desired, the composition can include about 0.05 to about .20 percent by weight of an antioxidant such as sodium metabisulfite or sodium bisulfite.

For intravenous administration, the composition preferably will be prepared so that the amount administered to the patient will be from about .01 to about 1 g of the conjugate. Preferably, the amount administered will be in the range of about .2 g to about 1 g of the conjugate. The conjugates of the invention are effective over a wide dosage range depending on factors such as the disease state to be treated or the biological effect to be modified, the manner in which the conjugate is administered, the age, weight and condition of the patient as well as

other factors to be determined by the treating physician. Thus, the amount administered to any given patient must be determined on an individual basis.

One skilled in the art will appreciate that although specific reagents and reaction conditions are outlined in the following examples, modification can be made which are meant to be encompassed by the spirit and scope of the invention. The following preparations and examples, therefore, are provided to further illustrate the invention, and are not limiting.

EXAMPLES

EXAMPLE 1

Identification of the Semenogelin PSA Mediated Cleavage Site: Liquefaction of the seminal gel parallels proteolytic fragmentation of semenogelin I [Lilja, H., Laurell, C.B., (1984) Scand. J. Clin. Lab. Inves. 44, 447-452]. It is believed that the proteolytic fragmentation of semenogelin is mainly due to the proteolytic activity of prostate-specific antigen [Lilja, H., (1985) J. Clin. Invest. 76, 1899-1903]. Utilizing the published sequence of semenogelin I [Lilja, H., Abrahamsson, P.A., Lundwall, A., (1989) J. of Biol. Chem. 264, 1894-1900] (Figure 1) we designed polymerase chain reaction primers to clone the semenogelin cDNA from a commercially available prostatic cDNA library (Clone-tech, Palo Alto, CA.). The purified semenogelin cDNA was placed into the bacterial expression vector pTAC [Linemeyer, D.L., Kelly, L.J., Minke, J.G., Gimenez-Gallego, G., DeSalvo, J. and Thomas, K.A., (1987) Bio/Technology 5, 960-965]. The semenogelin cDNA was designed so that a tubulin epitope was placed at the carboxyl end of semenogelin protein.. The bacterially expressed semenogelin protein was purified on an anti-tubulin antibody column. The purified semenogelin I protein was mixed with commercially prepared prostate-specific antigen (PSA) (York Biologicals International, Stony Brook, NY) in an 100 to 1 molar ratio (semenogelin I/PSA) in 12 mM Tris pH 8.0, 25 mM NaCl,

0.5 mM $CaCl_2$, and incubated for various times. The digest was fractionated by polyacrylamide gel electrophoresis and transferred by electrophoresis to ProBlott filter paper (Applied Biosystems, Inc., Foster City, CA.) in CAPS buffer [Matsudaira, P., (1987) J. Biol. Chem. 252, 10035-10038]. The ProBlott filter paper was stained with coomassie blue to identify the novel PSA generated semenogelin I protein fragments. The novel fragments were cut out of the filter with a scalpel and submitted for sequence determination. After the proteolytic fragments were identified by variable time digestion, a 10 minute digestion reaction was performed. The affinity of PSA for the 5 potential cleavage sites in semenogelin I was determined to be as follows: site 349/350 > site 375/376 > site 289/290 = site 315/316 > site 159/160. The relative affinities were derived from the comassie blue staining intensity of each PSA generated peptide fragment. These intensities had approximate ratios of 3:1:0.6:0.3.

EXAMPLE 2

Preparation of Oligopeptides which Comprise the PSA Mediated Cleavage Site:

Oligopeptides were prepared by solid-phase synthesis, using a double coupling protocol for the introduction of amino acids on the Applied Biosystems model 430A automated peptide synthesizer. Deprotection and removal of the oligopeptide from the resin support were achieved by treatment with liquid hydrofluoric acid. The oligopeptides were purified by preparative high pressure liquid chromatography on reverse phase C18 silica columns using an aqueous 0.1% trifluoroacetic acid/acetonitrile gradient. Identity and homogeneity of the oligopeptides were confirmed by amino acid composition analysis, high pressure liquid chromatography, and fast atom bombardment mass spectral analysis. The oligopeptides that were prepared by this method are shown in Figure 2.

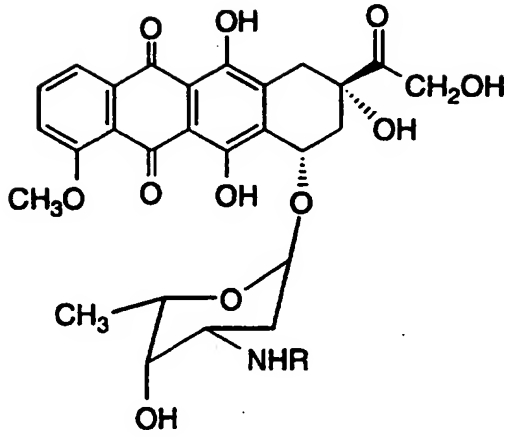
EXAMPLE 3

Assessment of the Recognition of Oligopeptides by Free PSA :
The oligopeptides prepared as described in Example 2 were individually dissolved in PSA digestion buffer (12 mM tris(hydroxymethyl)-aminomethane pH8.0, 25 mM NaCl, 0.5 mM $CaCl_2$) and the solution added to PSA at a molar ration of 100 to 1. Alternatively, the PSA digestion buffer utilized is 50 mM tris(hydroxymethyl)-aminomethane pH7.4, 140 mM NaCl. The reaction is quenched after various reaction times by the addition of trifluoroacetic acid (TFA) to a final 1% (volume/volume). Alternatively the reaction is quenched with 10mM $ZnCl_2$. The quenched reaction was analyzed by HPLC on a reversed-phase C18 column using an aqueous 0.1%TFA/acetonitrile gradient. The results of the assessment are shown in Figure 2. Other oligopeptides prepared as described in Example 2 were tested in the same assay wherein the reaction was quenched at 4 hours. Those results of the assessment are shown in Figure 3. The removal of an asparagine residue from the amino terminus of the oligopeptide results in a significant loss of PSA mediated peptide hydrolysis, while the presence of a glutamic acid residue at the carboxyl end of the peptide appears not to be essential to recognition by PSA.

EXAMPLE 4

Preparation of Non-cleavable Oligopeptide-Doxorubicin Conjugates:
The derivatives of doxorubicin shown in Table 3 were prepared using the following general reaction: To a mixture of doxorubicin (Sigma) and the corresponding peptide (prepared by solid phase synthesis or commercially available (Sigma)) in DMSO was added HBTU and HOBT along with diisopropylethylamine and the reaction mixture was stirred overnight. The crude reaction mixture was purified directly by preparative HPLC on a reversed-phase C-18 column using a 0.1% trifluoroacetic acid (TFA) in acetonitrile/0.1% TFA in water gradient.

Table 3



Compound	R	MS (parent ion)
12a	H-Ala-	615
12b	N-Ac-Ala-	657
12c	N-Ac-Ala-Ala-Ala-	799.5
12d	N-Ac-Ala-Gly-Pro-Thr-Gly-Ala-Ser-Ala-	1199

(SEQ.ID.NO.: 12)

EXAMPLE 5

In vitro Assay of Cytotoxicity of Peptidyl Derivatives of Doxorubicin: The cytotoxicities of the non-cleaveable oligopeptide-doxorubicin conjugates, prepared as described in Example 4, against a line of cells which is known to be killed by unmodified doxorubicin were assessed with an Alamar Blue assay. Specifically, cell cultures of LNCaP prostate tumor cells, which are a human metastatic prostate adenocarcinoma isolated from a needle biopsy of a lymph node (LNCaP.FGC: American Type Culture Collection, ATCC CRL 1740) , or DuPRO cells in 96 well plates were diluted with medium containing various concentrations of a given conjugate (final plate well volume of 200µl). The cells were

incubated for 3 days at 37°C and then 20µl of Alamar Blue was added to the assay well. The cells were further incubated and the assay plates were read on a EL-310 ELISA reader at the dual wavelengths of 570 and 600 nm at 4 and 7 hours after addition of Alamar Blue. Relative percentage viability at the various concentration of conjugate tested was then calculated versus control (no conjugate) cultures. Cytotoxicities of unmodified doxorubicin and unmodified oligopeptide were also assessed. Figure 3 shows the cytotoxicity data for a representative compound (Compound 12d).

EXAMPLE 6

Assessment of Enzymatically Active PSA from LNCaP Cells

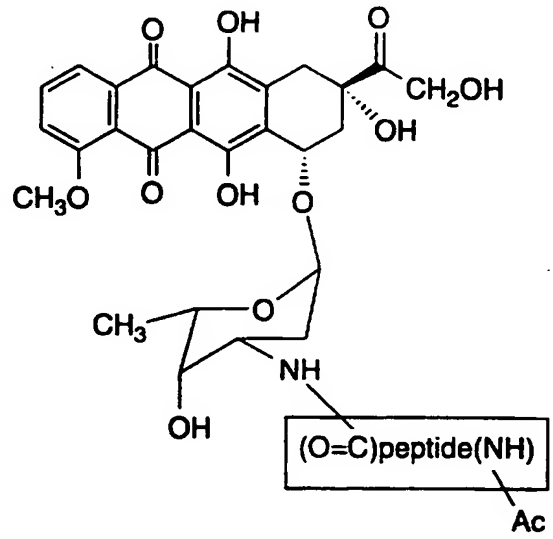
Enzymatic activity was demonstrated by incubating LNCaP serum free media (concentrated approximately 200 fold) with recombinant Sememogelin I protein. Approximately 0.5 µg of immunologically reactive PSA in concentrated conditioned media [determined by HYBRIDTECH (Tandem E) elisa] was mixed with approximately 3 µg of recombinant Semenogelin I and incubated for 4 hours at 37°C. At the end of the incubation, the digest mixture was analyzed by Western blot procedures. The results show that purified PSA from semen and PSA from LNCaP conditioned media generate identical proteolytic maps of the recombinant Semenogelin I protein. Thus, LNCaP cells produce enzymatically active PSA. LNCaP are tumorigenic in nude mice and produce detectable levels of circulating PSA.

EXAMPLE 7

Preparation of Cleavable Oligopeptide-Doxorubicin Conjugates:

The derivatives of doxorubicin wherein an oligopeptide which is proteolytically cleaved by free PSA is covalently attached to the amine of the sugar moiety of the doxorubicin were prepared using the following general reaction: To a mixture of doxorubicin (Sigma) and the corresponding peptide (prepared by solid phase synthesis as described in

Example 2) in DMSO was added HBTU and HOBT along with diisopropylethylamine and the reaction mixture stirred overnight. The crude reaction mixture was purified directly by preparative HPLC on a reversed-phase C-18 column using a 0.1% trifluoroacetic acid (TFA) in acetonitrile/0.1% TFA in water gradient. When reactive amine moieties were present on the peptide, such a functionality was typically protected as the fluorenylmethyloxycarbonyl adduct, which was removed by treatment with a secondary amine, such as piperidine and the like, subsequent to conjugation with doxirubicin. The instant conjugates have a structure of the general formula



and may be represented by the phrase "Ac-peptide-DOX (3')." Conjugates which were prepared by the above general method or by the synthetic route described in Example 8, but utilizing the appropriate starting amino acid residues which are readily available commercially or by synthetic techniques well known in the art, are listed in Tables 5, 5a and 7 in Figures 5, 5A and 7.

EXAMPLE 8

Ac-Lys-Tyr-Gln-Ser-Ser-Ser-Leu-Dox•Acetate

Step A: Ac-Lys(Fmoc)-Gln-Ser(Bzl)-Ser(Bzl)-Ser(Bzl)-Leu-PAM Resin (1).

Starting with 0.5 mmol (0.67g) Boc-Leu-PAM resin, the protected peptide was synthesized on a 430A ABI peptide synthesizer. The protocol used a 4 fold excess (2 mmol) of each of the following protected amino acids: Boc-Ser(OBzl), Boc-Gln, Boc-Tyr(BrZ), Boc-Lys(Fmoc). Coupling was achieved using DCC and HOBT activation in methyl-2-pyrrolidinone. Acetic acid was used for the introduction of the N terminal acetyl group. Removal of the Boc group was performed using 50% TFA in methylene chloride and the TFA salt neutralized with diisopropylethylamine. At the completion of the synthesis, the peptide resin was dried to yield 1.3g of (**1**).

Step B: Ac-Lys(Fmoc)-Tyr-Gln-Ser-Ser-Ser-Leu-OH (2)

The protected peptide resin (**1**), 1.3 g, was treated with HF (20 ml) for 2 hrs at 0°C in the presence of anisole (2 ml). After evaporation of the HF, the residue was washed with ether, filtered and extracted with DMF. The DMF filtrate (75 ml) was concentrated to dryness and triturated with H_2O. The insoluble product (**2**) was filtered and dried (0.46g).

Step C: Ac-Lys(Fmoc)-Tyr-Gln-Ser-Ser-Ser-Leu-Dox (3)

The above prepared intermediate (**2**), 0.46g, (0.43 mmol) was dissolved in DMF (15 ml) and doxorubicin hydrochloride, 125 mg (0.215 mmol), added followed by 60 µl of triethylamine (0.430 mmol). The stirred solution was cooled (0°C) and 92 µl of diphenylphosphoryl azide (0.43 mmol) added. After 5 minutes, an additional 92 µl of DPPA was added and the pH adjusted to ~7.5 (pH paper) with TEA. After 1 hour, an additional 92 µl of DPPA was added, pH adjusted to ~7.5, and the reaction stirred at 0°-5°C overnight. After 18 hours, the reaction (found to be complete by analytical HPLC) was concentrated to an oil (**3**).

Step D: Ac-Lys-Gln-Tyr-Ser-Ser-Ser-Leu-Dox (4).

The above product (3) was dissolved in DMF (20 ml), cooled (0°C) and 10 ml of piperidine added. The solution was concentrated to dryness and purified by preparative HPLC. Buffer A = 15% acetic acid-H_2O; B = 15% acetic acid-methanol. The crude product was dissolved in 300 ml of 10% B/90% A buffer, filtered and purified on a C-18 reverse phase HPLC radial compression column (Waters, Delta-Pak 15µm, 300Å). A step gradient of 10% B to 60% B was used at a flow rate of 75 ml/min (uv = 260 nm). Homogeneous product fractions were pooled, concentrated and freeze-dried from H_2O to yield 125 mg of purified product (4).

EXAMPLE 9

Deacetylvinblastinyl-Leu-Asn-Lys-Ala-Ser-Try-Gln-Ser-Ser-Ser-Leu-NH_2•Acetate (5) (SEQ.ID.NO. 184)

Step A: NH_2 - Leu-Asn-Lys(Fmoc)-Ala-Ser-Tyr-Gln-Ser-Ser-Ser-Leu-Amide (6)

Starting with 0.5 mmol of p-methylbenzhydrylamine resin (MBHA), the protected peptide, NH_2-Leu-Asn-Lys(Fmoc)-Ala-Ser(OBzl)-Tyr(BrZ)-Gln-Ser(OBzl)-Ser(OBzl)-Ser(OBzl)-Leu-MBHA, intermediate was synthesized on a 430A ABI peptide synthesizer. The protocol used a 4 fold excess (2 mmol) of each of the following protected amino acids: Boc-Leu, Boc-Asn, Boc-Lys (Fmoc), Boc-Ala, Boc-Ser(0Bzl), Boc-Tyr(BrZ), Boc-Gln. Coupling was achieved using DCC and HOBT activation in N-methyl-2-pyrrolidinone (NMP).

Removal of the Boc group was performed using 50% TFA in methylene chloride and the TFA salt neutralized with diisopropylethylamine. The dried protected peptide resin (1.80g) was treated with HF (20 ml) for 2 hrs at 0° C in the presence of anisole (2 ml). After evaporation, the residue was extracted with DMF. The DMF filtrate (75 ml) was concentrated to dryness, dissolved in a 1:1 mixture of acetonitrile-H_2O and freeze-dried to give 750 mg of crude product. A

portion (200 mg) was purified by preparative HPLC on a C-18 reverse phase support (Waters, μ-Bondapak). Buffer A = 15% acetic acid-H_2O; B = 15% acetic acid-methanol. For the purification, the crude product was suspended in 400 ml of 10% B/90% A buffer, filtered and the filtrate loaded onto the column. A step gradient of 10% B to 55% B was used at a flow rate of 75 ml/min. Homogeneous product fractions were pooled, concentrated and freeze-dried from H_2O to yield (**6**).

Step B: Deacetylvinblastin Monohydrazide (7)

1g of vinblastine sulfate was converted to the amine form by extraction in methylene chloride and saturated sodium bicarbonate. The methylene chloride layer was washed with H_2O, dried over anhydrous $MgSO_4$ and concentrated to dryness. The vinblastine was then dissolved in anhydrous ethanol (20 ml) and anhydrous hydrazine added (20 ml). The solution was heated (60° C) under an N_2 atmosphere for 17 hrs. The reaction was concentrated to an oil, dissolved in methylene chloride, extracted with H_2O and dried over $MgSO_4$. After evaporation compound (7) was isolated. [Ref: K.S.P. Bhushana Rao et al., J. Med. Chem. (1985), 28:1079.]

Step C: Deacetylvinblastine Acid Azide (8).

Deacetylvinblastine monohydrazide (7) (48 mg, 0.0624 mmol) was dissolved in DMF (3 ml), cooled (-15° C) and acidified to ~ 2.5 (pH paper) with HCl/dioxane. Isoamylnitrite (10 μl) was added followed by an additional 10 μl after 10 min. HPLC analysis indicated complete conversion of the hydrazide to azide after 5 min. The azide was maintained in solution at -15° C until ready for use.

Step D: Deacetylvinblastinyl-Leu-Asn-Lys-Ala-Ser-Try-Gln-Ser-Ser-Ser-Leu-NH_2•Acetate (5)

The oligopeptide product (**6**) from Step A, 32 mg (0.0225 mmol), was dissolved in DMF (1 ml) and cooled (-15° C). To this solution was added a 1.5 ml DMF solution (0.031 mmol) of desacetylvinblastine acid azide (**8**). The pH was adjusted to ~ 7.5 (pH

paper) with triethylamine and the reaction stirred at -5° C (2 hr), and 0° C for 18 hr. To the reaction was added H_2O (2 ml) and the solution evaporated to dryness. The intermediate was dissolved in DMF (4 ml), cooled (0° C) and 2 ml of piperidine added. The solution was concentrated to dryness and purified by preparative HPLC as described in Step A. The homogeneous fractions were pooled, concentrated and freeze-dried from H_2O to yield (**5**).

EXAMPLE 10

Deacetylvinblastinyl-Leu-Asn-Lys-Ala-Ser-Try-Gln-Ser-Ser-Ser-Leu--Dox •Acetate (**10**).

Step A: Deacetylvinblastinyl-Leu-Asn-Lys(Fmoc)-Ala-Ser-Try-Gln-Ser-Ser-Ser-Leu-Dox •Acetate (**9**)

The oligopeptide product (**6**) prepared as described in Example 9, Step A, (166 mg, 0.125 mmol), was dissolved in DMSO (3 ml) and cooled to -15° C. To this solution was added a DMF solution (0.125 mmol) of desacetylvinblastine acid azide (**8**) prepared as described in Example 9, Step C. The pH was adjusted to ~ 7.5 (pH paper) with triethylamine and the reaction stirred at -15° C for 90 mins.

After stirring 18 hours at 0-5° C, the reaction was concentrated to dryness and the crude residue was dissolved in DMF (10 ml) and filtered. Doxorubicin hydrochloride, 62 mg (0.106 mmol), was added to the filtrate followed by 30 µl of triethylamine. The stirred solution was cooled (0°C) and 27 µl of diphenylphosphoryl azide (DPPA, 0.134 mmol) added. After 5 minutes, an additional 27 µl of DPPA was added and the pH adjusted to ~7.5 (pH paper) with TEA. After 1 hour, an additional 27 µl of DPPA was added, pH adjusted to ~7.5, and the reaction stirred at 0°-5°C overnight. After 18 hours, the reaction (found to be complete by analytical HPLC) was concentrated to an oil (**9**).

Step B: Deacetylvinblastinyl-Leu-Asn-Lys-Ala-Ser-Try-Gln-Ser-Ser-Ser-Leu--Dox •Acetate (**10**).

The above intermediate product (**9**) was dissolved in DMF (20 ml), cooled (0°C) and 10 ml of piperidine added. The solution was concentrated to dryness and purified by preparative HPLC. Buffer A = 15% acetic acid-H_2O; B = 15% acetic acid-methanol. The crude product was dissolved in 300 ml of 10% B/90% A buffer, filtered and purified on a C-18 reverse phase HPLC radial compression column (Waters, μ-Bondapak). A step gradient of 10% B to 60% B was used at a flow rate of 75 ml/min (uv = 260 nm). Semi-pure product was further purified on C-18 (Waters, Prep Pak) using Buffer A = 0.13M pH 3.0 triethylammonium phosphate and Buffer B = acetonitrile. A step gradient of 10% B to 40% B was used at a flow rate of 75 ml/min. (uv = 214 nm). Pure product fractions were pooled, diluted with H_2O and desalted by applying the product onto the same column and eluting the product as the actetate salt with 90% acetonitrile/10% H_2O (1% acetic acid). The product fractions were concentrated and freeze dried from H_2O to yield the purified product (**10**).

EXAMPLE 11

Ac-Lys-Tyr-Gln-Ser-Ser-Ser-Nle-NH-$(CH_2)_3$ NH-deacetylvinblastine amide (**14**)

Step A: Deacetylvinblastine-3-aminopropyl amide (**11**)

To a cooled (-15° C) a DMF solution (3 ml, 0.0624 mmol) of deacetylvinblastine acid azide (synthesis described in Example 9, Step C) was added 120 μl of 1,3-diaminopropane in DMF (2 ml). The reaction was stirred at - 10° C for 1 hr, filtered and concentrated to dryness to yield (**11**).

Step B: Deacetylvinblastine-3-aminopropylamide-norleucine amide (**12**)

To a DMF solution (1 ml) of Boc-Nle (22 mg, 0.095 mmol) was added 318 μl of a 1M solution of HOBT (in NMP) followed by 280 μl of a 1M solution of DCC (in NMP). After 30 min., intermediate (**11**)

(0.0624 mmol) was added in a 3.5 ml DMF. The pH of the reaction was adjusted ~ 7.5 with diisopropylethylamine. After stirring for 18 hrs the reaction was concentrated to an oil and the Boc protecting group removed by treating the oil with a 1:1 solution of TFA: CH_2Cl_2 (20 ml). After 5 min. the reaction was concentrated to dryness. Purification was achieved by preparative HPLC on a C-18 reverse phase support (Waters, Delta Pak). Buffer A = 0.1% TFA-H_2O; B= 0.1% TFA-CH_3CN. The crude product was loaded in 100% A buffer (100 ml) and a step gradient of 100% A to 30% A was used at a flow rate of 75 ml/min. Homogeneous product fractions were pooled and freeze-dried to yield (**12**).

Step C: Ac-Lys(Fmoc)-Tyr-Gln-Ser-Ser-Ser-Nle-OH (**13**)
The above intermediate was prepared as described in Example 9, Step Afor the preparation of Ac-Lys(Fmoc)-Tyr-Gln-Ser-Ser-Ser-Leu-OH.

Step D: Ac-Lys-Tyr-Gln-Ser-Ser-Ser-Nle-NH-$(CH_2)_3$ NH-deacetylvinblastine amide (**14**)
The oligopeptide product (**13**), (70 mg, 0.065 mmol) in DMF (1 ml) was combined with (41 mg, 0.05 mmol) of (**12**) in DMF (4 ml). The solution was cooled (0° C) and 17 µl of diphenylphosphoryl azide (0.08 mmol) added. After 5 min. an additional 17 µl of DPPA was added and the pH adjusted to ~ 7.5 (pH paper) with triethylamine. After 2 hr. additional (**13**), 35 mg, was added in DMF (0.5 ml) and 17 µl of DPPA. The pH was maintained at ~ 7.5 with TEA and after 3 hr. an additional 35 mg of (**13**) was added in DMF (0.5 ml). The reaction was stirred at 0-5° C. After 18 hrs, the reaction was concentrated to dryness, redissolved in DMF (9 ml), cooled (0° C) and 3 ml of piperidine added. The solution was concentrated to dryness and purified by preparative HPLC. Buffer A = 0.1% TFA-H_2O; B= 0.1% TFA-CH_3 CN. The crude product was dissolved in 30% acetic acid - H_2O (100 ml) and purified on a C-18 reverse phase HPLC radial compression column (Waters, Delta Pak). A step gradient of 100% A to 70% A was used at a flow rate of 75 ml/min. Semi-pure product fractions were pooled and freeze-dried. Purification

to homogeneity was achieved by repurification on a C-4 support (Waters, Delta Pak) as described above. Product fractions were pooled and freeze dried to yield pure (**14**).

EXAMPLE 12

Assessment of the Recognition of Oligopeptide-Doxorubicin Conjugates by Free PSA :

The conjugates prepared as described in Examples 7-9 were individually dissolved in PSA digestion buffer (12 mM tris(hydroxymethyl)-aminomethane pH8.0, 25 mM NaCl, 0.5 mM $CaCl_2$) and the solution added to PSA at a molar ration of 100 to 1. Alternatively, the PSA digestion buffer utilized is 50 mM tris(hydroxymethyl)-aminomethane pH7.4, 140 mM NaCl. The reaction is quenched after various reaction times by the addition of trifluoroacetic acid (TFA) to a final 1% (volume/volume). Alternatively the reaction is quenched with 10mM $ZnCl_2$. The quenched reaction was analyzed by HPLC on a reversed-phase C18 column using an aqueous 0.1%TFA/acetonitrile gradient. The results of the assessment are shown in Tables 5 and 5a of Figure 5.

EXAMPLE 13

Assessment of the Cleavage of Oligopeptide-Doxorubicin Conjugates in Cell Conditioned Media :

Cell conditioned serum-free α–MEM media (phenol red minus) was collected 3 days after the addition of the media to either LNCaP or DuPRO (prepared as described in *J. Urology,* 146:915-919 (1991)) cell lines. The media was concentrated 20 fold using an Amicon® Centriprep™ concentrator with a 10,000 molecular weight cutoff. The LNCaP conditioned media contained free PSA protein at, on average, approximately 100 ng/mL concentration as determined by the Tandem®-E PSA immunodetection kit (Hybritech®). There was no detectable free PSA in the DuPRO cell conditioned media.

100 µL portions of concentrated conditioned media was mixed with 35 µg of a oligopeptide-doxorubicin conjugate prepared as described in Example 7 and the mixture was incubated at 37°C for 0, 4 and 24 hour time points. The reactions were stopped by the addition of $ZnCl_2$ (to a 0.01M final concentration) and analyzed by HPLC on a reversed-phase C18 column using an aqueous 0.1%TFA/acetonitrile gradient to determine the percentage of peptide-cytotoxic agent conjugate that had been digested. The results of the assessment are shown in Table 6 of Figure 6.

EXAMPLE 14

In vitro Assay of Cytotoxicity of Peptidyl Derivatives of Doxorubicin: The cytotoxicities of the cleaveable oligopeptide-doxorubicin conjugates, prepared as described in Example 7, against a line of cells which is known to be killed by unmodified doxorubicin was assessed with an Alamar Blue assay as described in Example 5. Specifically, cell cultures of LNCaP prostate tumor cells or DuPRO cells in 96 well plates was diluted with medium containing various concentrations of a given conjugate (final plate well volume of 200µl). The cells were incubated for 3 days at 37°C, 20µl of Alamar Blue is added to the assay well. The cells were further incubated and the assay plates were read on a EL-310 ELISA reader at the dual wavelengths of 570 and 600 nm at 4 and 7 hours after addition of Alamar Blue. Relative percentage viability at the various concentration of conjugate tested was then calculated versus control (no conjugate) cultures. Cytotoxicities of the conjugates were also compared to the cytotoxicity of unmodified doxorubicin and unmodified oligopeptide assessed in the same assay. Results of this assay are shown in Table 7 of Figure 7.

EXAMPLE 15

In vivo Efficacy of Peptidyl -Cytotoxic Agent Conjugates

LNCaP.FGC or DuPRO-1 cells are trypsinized, resuspended in the growth medium and centifuged for 6 mins. at 200xg. The cells are resuspended in serum-free α–MEM and counted. The appropriate volume of this solution containing the desired number of cells is then transferred to a conical centrifuge tube, centrifuged as before and resuspended in the appropriate volume of a cold 1:1 mixture of α–MEM-Matrigel. The suspension is kept on ice until the animals are inoculated.

Male nude mice (10-12 weeks old) are restrained without anesthesia and are inoculated with 0.5 mL of cell suspension on the left flank by subcutaneous injection using a 22G needle. Mice are either given approximately $5x10^5$ DuPRO cells or $1.5x10^7$ LNCaP.FGC cells.

Following inoculation with the tumor cells the mice are treated under one of two protocols:

Protocol A:

One day after cell inoculation the animals are dosed with a 0.1-0.5 mL volume of test conjugate, doxorubicin or vehicle control (sterile water). Dosages of the conjugate and doxorubicin are initially the maximum non-lethal amount, but may be subsequently titrated lower. Identical doses are administered at 24 hour intervals for 5 days. After 10 days, blood samples are removed from the mice and the serum level of PSA is determined. Similar serum PSA levels are determined at 5-10 day intervals. At the end of 5.5 weeks the mice are sacrificed and weights of any tumors present are measured and serum PSA again determined.The animals' weights are determined at the beginning and end of the assay.

Protocol B:

Ten days after cell inoculation,blood samples are removed from the animals and serum levels of PSA are determined. Animals are then grouped according to their PSA serum levels. At 14-15 days after cell

inoculation, the animals are dosed with a 0.1-0.5 mL volume of test conjugate, doxorubicin or vehicle control (sterile water). Dosages of the conjugate and doxorubicin are initially the maximum non-lethal amount, but may be subsequently titrated lower. Identical doses are administered at 24 hour intervals for 5 days. Serum PSA levels are determined at 5-10 day intervals. At the end of 5.5 weeks the mice are sacrificed, weights of any tumors present are measured and serum PSA again determined. The animals' weights are determined at the beginning and end of the assay.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

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Scolnick, Edward M.

(ii) TITLE OF INVENTION: CONJUGATES USEFUL IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

(iii) NUMBER OF SEQUENCES: 194

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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 462 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Met Lys Pro Asn Ile Ile Phe Val Leu Ser Leu Leu Leu Ile Leu Glu
1 5 10 15

Lys Gln Ala Ala Val Met Gly Gln Lys Gly Gly Ser Lys Gly Arg Leu
20 25 30

Pro Ser Glu Phe Ser Gln Phe Pro His Gly Gln Lys Gly Gln His Tyr
35 40 45

Ser Gly Gln Lys Gly Lys Gln Gln Thr Glu Ser Lys Gly Ser Phe Ser
50 55 60

Ile Gln Tyr Thr Tyr His Val Asp Ala Asn Asp His Asp Gln Ser Arg
65 70 75 80

Lys Ser Gln Gln Tyr Asp Leu Asn Ala Leu His Lys Thr Thr Lys Ser
85 90 95

Gln Arg His Leu Gly Gly Ser Gln Gln Leu Leu His Asn Lys Gln Glu
100 105 110

Gly Arg Asp His Asp Lys Ser Lys Gly His Phe His Arg Val Val Ile
115 120 125

His His Lys Gly Gly Lys Ala His Arg Gly Thr Gln Asn Pro Ser Gln
130 135 140

Asp Gln Gly Asn Ser Pro Ser Gly Lys Gly Ile Ser Ser Gln Tyr Ser
145 150 155 160

Asn Thr Glu Glu Arg Leu Trp Val His Gly Leu Ser Lys Glu Gln Thr
165 170 175

Ser Val Ser Gly Ala Gln Lys Gly Arg Lys Gln Gly Gly Ser Gln Ser
180 185 190

Ser Tyr Val Leu Gln Thr Glu Glu Leu Val Ala Asn Lys Gln Gln Arg
195 200 205

Glu Thr Lys Asn Ser His Gln Asn Lys Gly His Tyr Gln Asn Val Val
210 215 220

Glu Val Arg Glu Glu His Ser Ser Lys Val Gln Thr Ser Leu Cys Pro
225 230 235 240

Ala His Gln Asp Lys Leu Gln His Gly Ser Lys Asp Ile Phe Ser Thr
245 250 255

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Gln Asp Glu Leu Leu Val Tyr Asn Lys Asn Gln His Gln Thr Lys Asn
            260                 265                 270

Leu Asn Gln Asp Gln Gln His Gly Arg Lys Ala Asn Lys Ile Ser Tyr
        275                 280                 285

Gln Ser Ser Ser Thr Glu Glu Arg Arg Leu His Tyr Gly Glu Asn Gly
    290                 295                 300

Val Gln Lys Asp Val Ser Gln Ser Ser Ile Tyr Ser Gln Thr Glu Glu
305                 310                 315                 320

Lys Ala Gln Gly Lys Ser Gln Lys Gln Ile Thr Ile Pro Ser Gln Glu
                325                 330                 335

Gln Glu His Ser Gln Lys Ala Asn Lys Ile Ser Tyr Gln Ser Ser Ser
            340                 345                 350

Thr Glu Glu Arg Arg Leu His Tyr Gly Glu Asn Gly Val Gln Lys Asp
        355                 360                 365

Val Ser Gln Arg Ser Ile Tyr Ser Gln Thr Glu Lys Leu Val Ala Gly
    370                 375                 380

Lys Ser Gln Ile Gln Ala Pro Asn Pro Lys Gln Glu Pro Trp His Gly
385                 390                 395                 400

Glu Asn Ala Lys Gly Glu Ser Gly Gln Ser Thr Asn Arg Glu Gln Asp
                405                 410                 415

Leu Leu Ser His Glu Gln Lys Gly Arg His Gln His Gly Ser His Gly
            420                 425                 430

Gly Leu Asp Ile Val Ile Ile Glu Gln Glu Asp Asp Ser Asp Arg His
        435                 440                 445

Leu Ala Gln His Leu Asn Asn Asp Arg Asn Pro Leu Phe Thr
    450                 455                 460
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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Gly Lys Gly Ile Ser Ser Gln Tyr Ser Asn Thr Glu Glu Arg Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Asn Lys Ile Ser Tyr Gln Ser Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Gly Glu Asn Gly Val Gln Lys Asp Val Ser Gln Arg Ser Ile Tyr Ser
1 5 10 15

Gln Thr Glu

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Gly Glu Asn Gly Val Gln Lys Asp Val Ser Gln Ser Ser Ile Tyr Ser
1 5 10 15

Gln Thr Glu

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Gly Arg Lys Ala Asn Lys Ile Ser Tyr Gln Ser Ser Ser Thr Glu Glu
1 5 10 15

Arg Arg Leu His Tyr Gly Glu Asn Gly
20 25

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Ser Tyr Gln Ser Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Ile Ser Tyr Gln Ser Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Lys Ile Ser Tyr Gln Ser Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Asn Lys Ile Ser Tyr Gln Ser Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Ala Asn Lys Ile Ser Tyr Gln Ser Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Ala Gly Pro Thr Gly Ala Ser Ala
1 5

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Asn Lys Ile Ser Tyr Gln Ser
1 5

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Lys Ile Ser Tyr Gln Ser
1 5

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 12
(D) OTHER INFORMATION: /note= "any natural amino acid"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Gly Glu Asn Gly Val Gln Lys Asp Val Ser Gln Xaa Ser Ile Tyr Ser
1 5 10 15

Gln Thr Glu

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Asn Lys Ile Ser Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Asn Lys Ile Ser Tyr Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Ala Asn Lys Ile Ser Tyr Gln Ser Ser Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Lys Ile Ser Tyr Gln Ser Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Gln Leu Asp Asn Lys Ile Ser Tyr Gln Ser Ser Ser Thr His Gln Ser
1 5 10 15

Ser

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Asn Arg Ile Ser Tyr Gln Ser
1 5

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Asn Lys Val Ser Tyr Gln Ser
1 5

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Asn Lys Met Ser Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Asn Lys Leu Ser Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Asn Lys Ile Thr Tyr Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Asn Lys Ile Ser Phe Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Asn Lys Ile Ser Trp Gln Ser Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Asn Lys Ile Ser Tyr Asn Ser Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Asn Lys Ile Ser Tyr Gln Thr Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Asn Lys Ile Ser Tyr Gln Ser
1 5

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Gln Lys Ile Ser Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Asn Arg Ile Thr Tyr Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Asn Arg Ile Ser Phe Gln Ser Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Gln Lys Ile Ser Tyr Gln Thr Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Asn Arg Ile Ser Trp Gln Ser Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Asn Arg Ile Ser Tyr Gln Thr Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Asn Lys Ile Thr Tyr Gln Thr Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Asn Lys Leu Ser Tyr Gln Thr Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Gln Lys Leu Ser Tyr Gln Ser Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Asn Arg Leu Ser Tyr Gln Thr Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Asn Lys Val Ser Phe Gln Ser Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Asn Arg Val Ser Trp Gln Ser Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Gln Lys Val Ser Tyr Gln Ser Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Asn Lys Ile Ser Tyr Gln Ser Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Gly Glu Gln Gly Val Gln Lys Asp Val Ser Gln Ser Ser Ile Tyr Ser
1 5 10 15

Gln Thr Glu

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

Gly Lys Gly Ile Ser Ser Gln Tyr Ser Asn Thr Asp Glu Arg Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

Gly Glu Asn Gly Leu Gln Lys Asp Val Ser Gln Ser Ser Ile Tyr Ser
1 5 10 15

Gln Thr Glu

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Gly Glu Asn Gly Val Asn Lys Asp Val Ser Gln Ser Ser Ile Tyr Ser
1 5 10 15

Gln Thr Glu

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

Gly Glu Asn Gly Val Gln Arg Asp Val Ser Gln Arg Ser Ile Tyr Ser
1 5 10 15

Gln Thr Glu

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Gly Glu Asn Gly Val Gln Lys Asp Val Ser Gln Lys Ser Ile Tyr Ser
1 5 10 15

Gln Thr Glu

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Gly Glu Asn Gly Val Gln Lys Asp Leu Ser Gln Thr Ser Ile Tyr Ser
1 5 10 15

Gln Thr Glu

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

Gly Glu Asn Gly Val Gln Lys Asp Val Ser Gln Ser Ser Ile Phe Ser
1 5 10 15

Gln Thr Glu

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Gly Glu Asn Gly Val Gln Lys Asp Met Ser Gln Ser Ser Ile Tyr Thr
1 5 10 15

Gln Thr Glu

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:
Gly Glu Asn Gly Val Gln Lys Asp Val Ser Gln Arg Ser Ile Tyr Thr
1 5 10 15

Gln Thr Glu

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Gly Glu Asn Gly Val Gln Lys Asp Val Ser Gln Ser Ser Ile Tyr Ser
1 5 10 15

Gln Ser Glu

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Gly Glu Asn Gly Val Gln Lys Asp Val Ser Gln Arg Ser Ile Tyr Ser
1 5 10 15

Asn Thr Glu

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Gly Lys Ala Ile Ser Ser Gln Tyr Ser Asn Thr Glu Glu Arg Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Gly Lys Gly Ile Ser Ser Gln Tyr Ser Asn Ser Glu Glu Arg Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Gly Arg Gly Ile Ser Ser Gln Tyr Ser Asn Thr Glu Glu Arg Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Gly Lys Gly Ile Thr Ser Gln Tyr Ser Asn Thr Glu Glu Arg Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Gly Lys Gly Ile Ser Thr Gln Tyr Ser Asn Thr Glu Glu Arg Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Gly Lys Gly Ile Ser Ser Asn Tyr Ser Asn Thr Glu Glu Arg Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Ala Lys Gly Ile Ser Ser Gln Tyr Ser Asn Thr Glu Glu Arg Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

Gly Lys Gly Ile Ser Ser Gln Phe Ser Asn Thr Glu Glu Arg Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

Gly Lys Gly Ile Ser Ser Gln Tyr Thr Asn Ser Glu Glu Arg Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Gly Lys Gly Ile Ser Ser Gln Tyr Ser Asn Ser Glu Glu Arg Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Ser Gln Lys Ala Asn Lys Ile Ser Tyr Gln Ser Ser Ser Thr Glu Glu
1 5 10 15

Arg Arg Leu His Tyr Gly Glu Asn Gly
20 25

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

Ile Ser Tyr Gln Ser Ser Ser Thr
1 5

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Ala Asn Lys Ile Ser Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Ala Asn Lys Ile Ser Tyr Gln Ser Ser Ser Thr Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Ala Asn Gly Ile Ser Tyr Gln Ser Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Ala Asn Pro Ile Ser Tyr Gln Ser Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

Ala Asn Lys Ile Ser Tyr Gln Ser Ala Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Ala Asn Lys Ile Ser Tyr Gln Ser Ser Lys Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Ala Asn Lys Ile Ser Tyr Gln Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 5
(D) OTHER INFORMATION: /label= d-serine
/note= "unnatural configuration of the amino acid"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

Ala Asn Lys Ile Ser Tyr Gln Ser Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide

(B) LOCATION: 4
(D) OTHER INFORMATION: /label= d-isoleucine
/note= "unnatural amino acid stereochemical configuration"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

Ala Asn Lys Ile Ser Tyr Gln Ser Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

Ala Asn Lys Ile Ser Tyr Gln Ser Ser Gln Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Ala Asn Lys Ile Ser Tyr Gln Ser Ala Lys Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 3
(D) OTHER INFORMATION: /label= d-lysine
/note= "unnatural amino acid stereochemical configuration"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

Ala Asn Lys Ile Ser Tyr Gln Ser Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

Ala Asn Lys Ile Ser Tyr Gln Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

Ala Asn Lys Ser Tyr Gln Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

Ala Asn Lys Ile Tyr Gln Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

Ala Asn Lys Ala Ser Tyr Gln Ser Ala Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

Ala Asn Glu Ile Ser Tyr Gln Ser Ala Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

Lys Ile Ser Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

Ser Tyr Gln Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

Ser Tyr Gln Ser Ser Thr Leu
1 5

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

Ala Ser Tyr Gln Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Glu Ile Ser Tyr Gln Ser Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

Ala Asn Glu Ile Ser Tyr Gln Ser Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

Ala Asn Lys Ile Ser Tyr Tyr Ser Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

Ala Asn Lys Ile Ser Tyr Tyr Ser Ala Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

Ala Ser Tyr Gln Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

Ala Asn Ser Tyr Gln Ser Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

Ala Ser Tyr Gln Ser Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

Ser Tyr Gln Ser Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

Ala Asn Lys Ala Ser Tyr Gln Ser Ala Ser Thr Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

Gln Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

Tyr Gln Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

Ser Gln Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

Ala Asn Lys Ile Ser Gln Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 3
(D) OTHER INFORMATION: /label= unnatural
/note= "ornithine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

Ala Asn Xaa Ile Ser Tyr Gln Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /label= unnatural
/note= "3,4-dichlorophenalanine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

Ser Xaa Gln Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /label= unnatural
/note= "(3-pyridinyl)alanine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

Ser Xaa Gln Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

Ser Lys Gln Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

Ser Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /label= unnatural
/note= "epsilon aminocaproic acid"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

Xaa Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 4
(D) OTHER INFORMATION: /label= unnatural
/note= "N-methylisoleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

Ala Asn Lys Xaa Ser Tyr Gln Ser Ser Thr Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

Ser Tyr Gln Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

Tyr Gln Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

Ser Tyr Lys Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

Ser Tyr Tyr Ser Ser Thr Glu
1 5

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

Ser Tyr Gln Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

Ser Tyr Gln Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /label= unnatural
/note= "2,3-diaminopropionic acid"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

Xaa Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

Ala Asn Lys Ile Ser Tyr Gln Ser Ser Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

Ala Asn Lys Ala Ser Tyr Gln Ser Ala Ser Thr Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

Ala Asn Lys Ala Ser Tyr Gln Ser Ala Ser Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

Ala Asn Lys Ala Ser Tyr Gln Ser Ser Ser Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

Ala Asn Lys Ala Ser Tyr Gln Ser Ser Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /label= d-leucine
/note= "unnatural amino acid stereochemical configuration"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

Ser Tyr Gln Ser Ser Thr Leu
1 5

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

Ala Asn Lys Ala Ser Tyr Ala Ser Ser Ser Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

Lys Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Ser Tyr Gln Ser Ser Lys Leu
1 5

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /label= d-leucine
/note= "unnatural amino acid stereochemical configuration"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

Ser Tyr Gln Ser Ser Lys Leu
1 5

(2) INFORMATION FOR SEQ ID NO:127:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

Asn Lys Ile Ser Tyr Tyr Ser
1 5

(2) INFORMATION FOR SEQ ID NO:128:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

Asn Lys Ala Ser Tyr Gln Ser
1 5

(2) INFORMATION FOR SEQ ID NO:129:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

Ser Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

Asn Lys Ile Ser Tyr Gln Ser Ala
1 5

(2) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

Ala Asn Lys Ile Ser Tyr Tyr Ser
1 5

(2) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

Ala Asn Lys Ala Ser Tyr Gln Ser
1 5

(2) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

Ser Tyr Gln Ser Ser Thr
1 5

(2) INFORMATION FOR SEQ ID NO:134:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

Ser Tyr Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:135:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

Ser Tyr Gln Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:136:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGME TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

Ala Asn Lys Ile Ser Tyr Gln Ser Ala
1 5

(2) INFORMATION FOR SEQ ID NO:137:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

Ala Asn Lys Ile Ser Tyr Tyr Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:138:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:

Ala Asn Lys Ile Ser Tyr Tyr Ser Ala
1 5

(2) INFORMATION FOR SEQ ID NO:139:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

Ala Asn Lys Ala Ser Tyr Gln Ser Ala
1 5

(2) INFORMATION FOR SEQ ID NO:140:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

Lys Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:141:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /label= homoarginine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:141:

Xaa Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:142:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:

Lys Tyr Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:143:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /label= homoarginine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:

Xaa Tyr Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:144:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:144:

Ser Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:145:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /label= homoarginine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:

Xaa Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:146:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /label= norleucine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:

Lys Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:147:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "cyclohexylalanine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 5
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:147:

Xaa Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:148:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "homotyrosine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 6
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:148:

Xaa Xaa Gln Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:149:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "cyclohexylhomoalanine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 6
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:149:

Xaa Xaa Gln Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:150:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 10
(D) OTHER INFORMATION: /product= "cyclohexylalanine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:150:

Ala Asn Lys Ala Ser Tyr Gln Ser Ser Xaa
1 5 10

(2) INFORMATION FOR SEQ ID NO:151:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:151:

Xaa Tyr Gln Ser Ser Pro
1 5

(2) INFORMATION FOR SEQ ID NO:152:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:152:

Xaa Tyr Gln Ser Ser His
1 5

(2) INFORMATION FOR SEQ ID NO:153:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:153:

Xaa Tyr Gln Ser Asn
1 5

(2) INFORMATION FOR SEQ ID NO:154:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:154:

Xaa Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:155:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product=
"4-aminomethylphenylalanine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:155:

Xaa Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:156:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:156:

Xaa Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:157:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 10
(D) OTHER INFORMATION: /product= "cyclohexylalanine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:157:

Ala Asn Lys Ala Lys Tyr Gln Ser Ser Xaa
1 5 10

(2) INFORMATION FOR SEQ ID NO:158:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product=
"2(4,6-dimethylpyrimidine)lysine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:158:

Xaa Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:159:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "N'-(2-imidazolyl)lysine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:159:

Xaa Tyr Gln Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:160:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 5
(D) OTHER INFORMATION: /product= "homoarginine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:160:

Ala Asn Lys Ala Xaa Tyr Gln Ser Ser Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:161:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product=
"(4-aminocyclohexyl)alanine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:161:

Xaa Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:162:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "N'-(2-imidazolyl)lysine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ NO:162:

Xaa Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:163:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "cyclohexylalanine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:163:

Xaa Xaa Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:164:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "homoarginine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:164:

Xaa Tyr Gln Ser Ser Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:165:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 5
(D) OTHER INFORMATION: /product= "N'-(2-imidazolyl)lysine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 10
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:165:

Ala Asn Lys Ala Xaa Tyr Gln Ser Ser Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:166:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "3-iodotyrosine"

(ix) FEATURE:
(A) NAME/KEY: Peptide

(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:166:

Xaa Xaa Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:167:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product=
"O-dimethylphosphotyrosine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:167:

Xaa Xaa Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:168:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1

(D) OTHER INFORMATION: /product= "homoarginine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:168:

Xaa Tyr Gln Ser Ser Asp
1 5

(2) INFORMATION FOR SEQ ID NO:169:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "O-methyltyrosine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:169:

Xaa Xaa Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:170:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 10
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:170:

Ala Asn Lys Ala Lys Tyr Gln Ser Ser Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:171:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "cyclohexylalanine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:171:

Xaa Xaa Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:172:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "N'-(2-imidazolyl)lysine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "cyclohexylalanine"

(ix) FEATURE:
(A) NAME/KEY: Peptide

(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:172:

Xaa Xaa Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:173:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "cyclohexylalanine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:173:

Xaa Xaa Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:174:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "cyclohexylalanine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 6
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:174:

Xaa Xaa Gln Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:175:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "cyclohexylalanine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 6
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:175:

Xaa Xaa Gln Ser Pro Leu
1 5

(2) INFORMATION FOR SEQ ID NO:176:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "3-fluorotyrosine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:176:

Xaa Xaa Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:177:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:177:

Xaa Tyr Gln Ser Pro
1 5

(2) INFORMATION FOR SEQ ID NO:178:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 6

(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:178:

Lys Tyr Gln Ser Lys Leu
1 5

(2) INFORMATION FOR SEQ ID NO:179:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "4-aminophenylalanine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:179:

Xaa Xaa Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:180:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product=
"7-HO-tetrahydroisoquinoline CO2H"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:180:

Xaa Xaa Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:181:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "ornithine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:181:

Xaa Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:182:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:182:

Lys Ala Ala Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:183:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 7
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:183:

Lys Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:184:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:184:

Leu Asn Lys Ala Ser Tyr Gln Ser Ser Ser Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:185:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 2
(D) OTHER INFORMATION: /product= "cyclohexylalanine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:185:

Xaa Xaa Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:186:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:186:

Tyr Gln Ser Ser
1

(2) INFORMATION FOR SEQ ID NO:187:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:187:

Xaa Tyr Gln Ser
1

(2) INFORMATION FOR SEQ ID NO:188:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "homoarginine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:188:

Xaa Tyr Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:189:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 5
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:189:

Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:190:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product=
"7-HO-tetrahydro-3-isoquinoline CO2H"

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 6
(D) OTHER INFORMATION: /product= "norleucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:190:

Xaa Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:191:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:191:

Ala Asn Lys Ala Ser Tyr Ala Ser Ser Ser Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:192:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:192:

Ser Tyr Gln Ser Ser Lys Leu
1 5

(2) INFORMATION FOR SEQ ID NO:193:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:193:

Ala Asn Lys Ala Ser Tyr Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:194:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1
(D) OTHER INFORMATION: /product= "ornithine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:194:

Xaa Tyr Gln Ser Ser Ser Leu
1 5

WHAT IS CLAIMED IS:

1. A method of treating an adverse condition of the prostate which comprises administering to a mammal in need of said treatment a conjugate, said conjugate which comprises a pharmaceutical agent, effective in the treatment of said condition, attached to an oligopeptide, wherein the oligopeptide comprises a sequence of amino acids that is recognized and selectively proteolytically cleaved by free prostate specific antigen, wherein the means of attachment is directly through a covalent bond or via a linker unit,

or the pharmaceutically acceptable salt thereof.

2. A method of treating benign prostatic hyperplasia which comprises administering to a mammal in need of said treatment a conjugate, said conjugate which comprises a cytotoxic agent attached to a oligopeptide, wherein the oligopeptide comprises a sequence of amino acids that is recognized and selectively proteolytically cleaved by free prostate specific antigen, wherein the means of attachment is directly through a covalent bond or via a linker unit,

or the pharmaceutically acceptable salt thereof.

3. The method of treatment according to Claim 2 wherein the cytotoxic agent is a member of a class of cytotoxic agents selected from the following classes:

a) anthracycline family of drugs,
b) the vinca alkaloid drugs,
c) the mitomycins,
d) the bleomycins,
e) the cytotoxic nucleosides,
f) the pteridine family of drugs,
g) diynenes,
h) estramustine,

i) cyclophosphamide,
j) the podophyllotoxins, and
k) the taxanes;

or the pharmaceutically acceptable salt thereof.

4. The method of treatment according to Claim 2 wherein the cytotoxic agent is selected from the following cytotoxic agents:

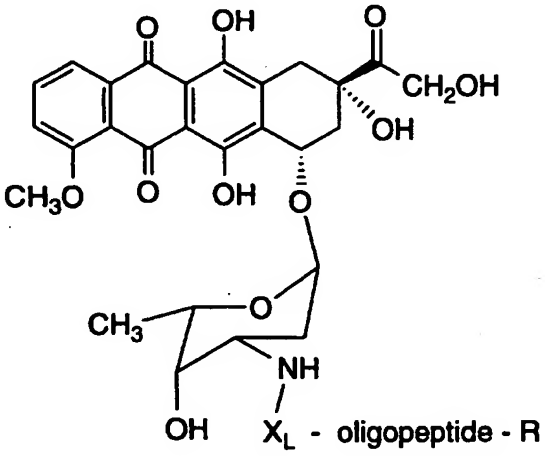
a) doxorubicin,
b) carminomycin,
c) daunorubicin,
d) aminopterin,
e) methotrexate,
f) methopterin,
g) dichloro-methotrexate,
h) mitomycin C,
i) porfiromycin,
j) 5-fluorouracil,
k) 6-mercaptopurine,
l) cytosine arabinoside,
m) podophyllotoxin,
n) etoposide,
o) etoposide phosphate,
p) melphalan,
q) vinblastine,
r) vincristine,
s) leurosidine,
t) vindesine,
u) estramustine,
v) cisplatin,
w) cyclophosphamide,
x) leurosine, and
y) taxol;

or the pharmaceutically acceptable salt thereof.

5. The method of treatment according to Claim 2 wherein the cytotoxic agent is selected from doxorubicin, vinblastine and desacetylvinblastine or a cytotoxic derivative thereof.

6. The method of treatment according to Claim 2 wherein the cytotoxic agent is selected from vinblastine and desacetylvinblastine or a cytotoxic derivative thereof.

7. The method of treatment according to Claim 5 wherein the conjugate is of the formula I:



I

wherein:

oligopeptide is an oligopeptide which is specifically recognized by the free prostate specific antigen (PSA) and is capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen;

X_L is absent or is an amino acid selected from:

a) phenylalanine,
b) leucine,
c) valine,
d) isoleucine,
e) (2-naphthyl)alanine,
f) cyclohexylalanine,
g) diphenylalanine,
h) norvaline, and
i) norleucine, and
j) 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;

R is hydrogen or -(C=O)R^1; and

R^1 is C_1-C_6-alkyl or aryl,

or the pharmaceutically acceptable salt thereof.

8. The method of treatment according to Claim 7 wherein:

oligopeptide is an oligomer that comprises an amino acid sequence selected from:

a) AsnLysIleSerTyrGlnlSer (SEQ.ID.NO.: 13),

b) LysIleSerTyrGlnlSer (SEQ.ID.NO.: 14),

c) GlyGluAsnGlyValGlnLysAspValSerGlnXaaSerIleTyrlSerGlnThrGlu (SEQ.ID.NO.: 15),

d) GlyLysGlyIleSerSerGlnTyrlSerAsnThrGluGluArgLeu (SEQ.ID.NO.: 2),

e) AsnLysIleSerTyrTyrlSer (SEQ.ID.NO.: 127),

f) AsnLysAlaSerTyrGlnlSer (SEQ.ID.NO.: 128),

g) SerTyrGlnlSerSer (SEQ.ID.NO.: 129),

h) LysTyrGlnlSerSer (SEQ.ID.NO.: 140);

i) hArgTyrGlnlSerSer (SEQ.ID.NO.: 141);

j) hArgChaGlnlSerSer (SEQ.ID.NO.: 185); and

k) TyrGlnlSerSer (SEQ.ID.NO.: 186);

wherein hArg is homoarginine and Xaa is any natural amino acid;

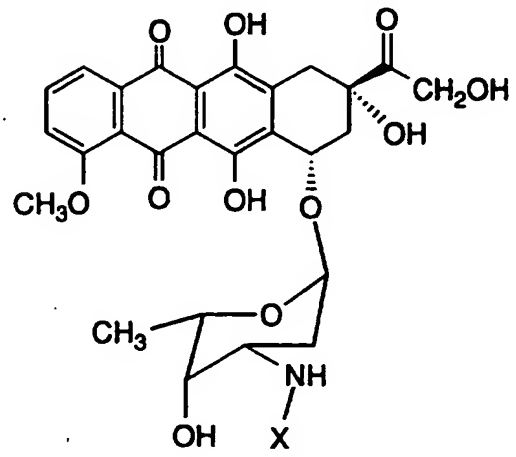
X_L is absent or is an amino acid selected from:

a) leucine,
b) isoleucine,
c) norleucine and
d) valine; and

R is acetyl, pivaloyl or benzoyl,

or the pharmaceutically acceptable salt thereof.

9. The method of treatment according to Claim 7 wherein the conjugate is selected from:



wherein X is:

AsnLysIleSerTyrGlnSer— (SEQ.ID.NO.: 13),

AsnLysIleSerTyrGlnSerSer— (SEQ.ID.NO.: 16),

AsnLysIleSerTyrGlnSerSerSer — (SEQ.ID.NO.: 17),

AsnLysIleSerTyrGlnSerSerSerThr — (SEQ.ID.NO.:10),

AsnLysIleSerTyrGlnSerSerSerThrGlu — (SEQ.ID.NO.: 3),

AlaAsnLysIleSerTyrGlnSerSerSerThrGlu — (SEQ.ID.NO.: 11),

N-terminus

Ac—AlaAsnLysIleSerTyrGlnSerSerSerThr— (SEQ.ID.NO.: 117),

Ac—AlaAsnLysIleSerTyrGlnSerSerSerThrLeu— (SEQ.ID.NO.: 70),

Ac—AlaAsnLysAlaSerTyrGlnSerAlaSerThrLeu— (SEQ.ID.NO.: 118),

Ac—AlaAsnLysAlaSerTyrGlnSerAlaSerLeu— (SEQ.ID.NO.: 119),

Ac—AlaAsnLysAlaSerTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 120),

Ac—AlaAsnLysAlaSerTyrGlnSerSerLeu— (SEQ.ID.NO.: 121),

Ac—SerTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 144),

Ac—hArgTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 145),

Ac—LysTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 124), or

Ac—LysTyrGlnSerSerNle— (SEQ.ID.NO.: 146),

N-terminus

or the pharmaceutically acceptable salt thereof.

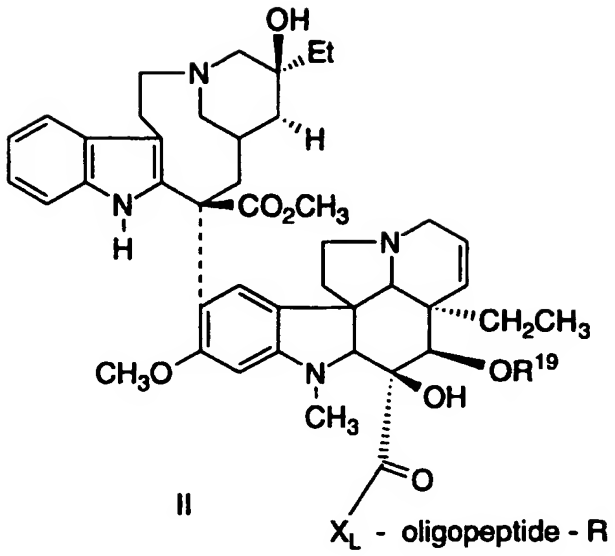
10. The method of treatment according to Claim 7 wherein the conjugate is selected from:

Ac-hArgTyrGln-SerSerPro-dox(3') (SEQ.ID.NO.: 151)
Ac-hArgTyrGln-SerPro-dox(3') (SEQ.ID.NO.: 177)
Ac-hArgTyrGln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 154)
Ac-AmfTyrGln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 155)
H_2NCO-hArgTyrGln-SerSerSerLeu-dox(3') (SEQ.ID.NO.: 156)

Ac-LysTyrGln-SerSerNle-dox(3') (SEQ.ID.NO.: 146)
Ac-LysTyrGln-SerLysNle-dox(3') (SEQ.ID.NO.: 178)
Ac(cis-p-NH_2Cha)TyrGlnSerSerNledox(3') (SEQ.ID.NO.: 161)
Ac-AlaAspLysAla(hArg)TyrGln-SerSerLeu-dox(3') (SEQ.ID.NO.: 160)
Ac-hArgTyrGln-SerAsn-dox(3') (SEQ.ID.NO.: 153)
Ac-hArgTyrGln-SerSerHis-dox(3') (SEQ.ID.NO.: 152)
Ac-(imidazolyl)LysTyrGln-SerSerLeu-dox(3') (SEQ.ID.NO.: 159)
Ac-(imidazolyl)LysTyrGlnSerSerSerNle-dox(3') (SEQ.ID.NO.: 162)
Ac-hArg(Cha)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 163)
Ac-hArg(Me_2PO_3Tyr)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 167)
Ac-hArgTyrGln-SerSerSerhArg-dox(3') (SEQ.ID.NO.: 164)
Ac-hArg(3-Iodo-Tyr)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 166)
Ac-hArg(O-Me-Tyr)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 169)
Ac-hArg(p-NH_2-Phe)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 179)
Ac-hArg(Cha)Gln-SerSerNle-dox(3') (SEQ.ID.NO.: 174)
Ac-hArg(Cha)Gln-SerProNle-dox(3') (SEQ.ID.NO.: 175)
Ac(imidazolyl)Lys(Cha)GlnSerSerSerNle-dox(3') (SEQ.ID.NO.: 172)
Ac-hArg(7-HO-TIC)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 180)
Ac-hArg(3-Fluoro)TyrGlnSerSerSerNle-dox(3') (SEQ.ID.NO.: 176)
Ac-(ornithine)TyrGln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 181)
Ac-LysAlaAlaSerSerSerLeu-dox(3') (SEQ.ID.NO.: 183)
Ac-hArgh(Cha)Gln-SerSerNle-dox(3') (SEQ.ID.NO.: 149)
Ac-AlaArgLysAlaSerTyrGln-SerLeu-dox(3') (SEQ.ID.NO.: 193) and
Ac-(Orn)TyrGln-SerSerSerLeu-dox(3') (SEQ.ID.NO.: 194)

or the pharmaceutically acceptable salt thereof.

11. The method of treatment according to Claim 6 wherein the conjugate is of the formula II:



II

wherein:

oligopeptide is an oligopeptide which is specifically recognized by the free prostate specific antigen (PSA) and is capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen;

X_L is absent or is an amino acid selected from:

a) phenylalanine,
b) leucine,
c) valine,
d) isoleucine,
e) (2-naphthyl)alanine,
f) cyclohexylalanine,
g) diphenylalanine,
h) norvaline,
i) norleucine, and
j) 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; or

X_L is - NH - $(CH_2)_n$ - NH -

R is hydrogen or -(C=O)R^1;

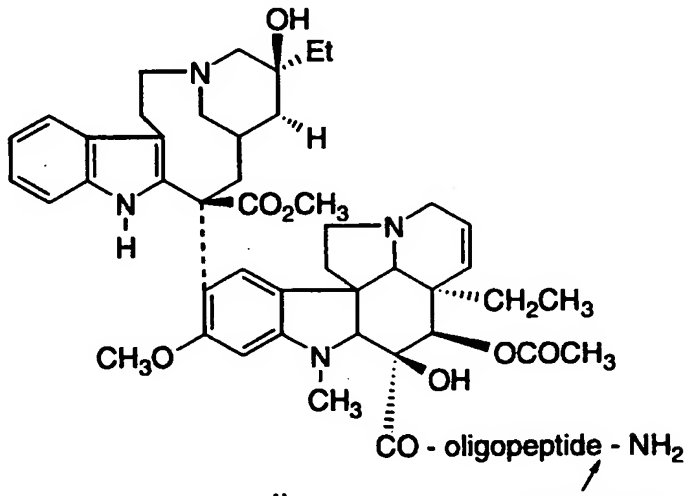
R^1 is C_1-C_6-alkyl or aryl;

R^{19} is hydrogen or acetyl; and

n is 1, 2, 3, 4 or 5,

or the pharmaceutically acceptable salt thereof.

12. The method of treatment according to Claim 11 wherein the conjugate is of the formula II:



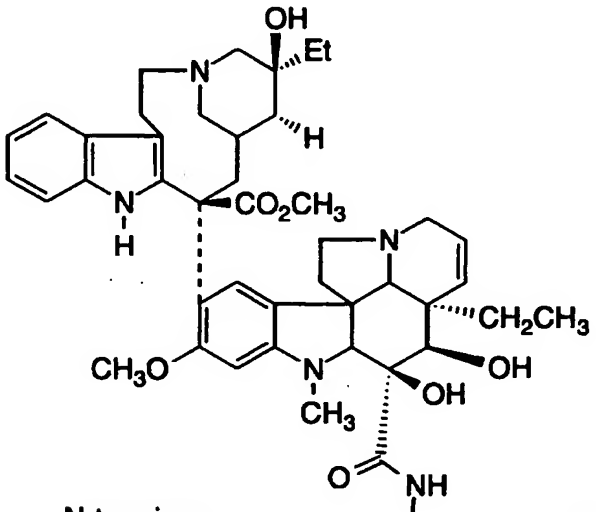
II

wherein:

oligopeptide is an oligopeptide which is specifically recognized by the free prostate specific antigen (PSA) and is capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen,

or the pharmaceutically acceptable salt thereof.

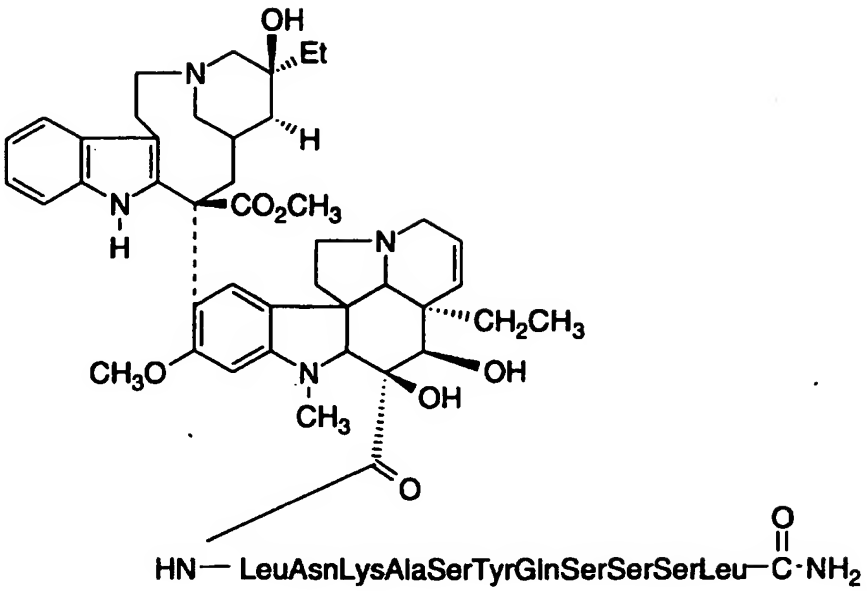
13. The method of treatment according to Claim 11 wherein the conjugate is selected from:



Compound 14

Ac— LysTyrGlnSerSerSerNle —NH (SEQ.ID.NO.: 183),

and



Compound 5 (SEQ.ID.NO.: 184),

or the pharmaceutically acceptable salt thereof.

14. A method of treating an adverse condition of the prostate which comprises administering to a mammal in need of said treatment a conjugate, said conjugate which comprises two pharmaceutical agents, wherein at least one pharmaceutical agent is effective against said condition, attached to a oligopeptide, wherein the oligopeptide comprises a sequence of amino acids that is recognized and selectively proteolytically cleaved by free prostate specific antigen, wherein the means of attachment is directly through a covalent bond or via a linker unit,

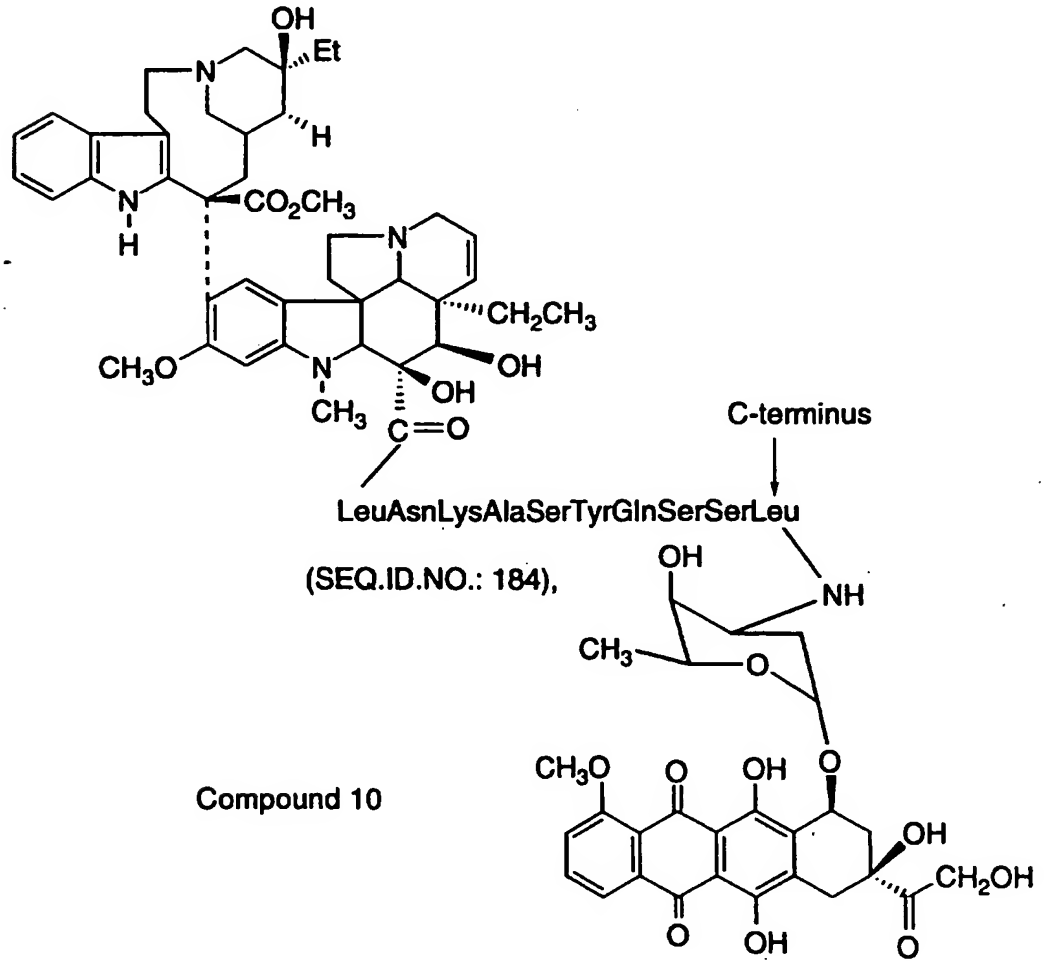
or the pharmaceutically acceptable salt thereof.

15. A method of treating benign prostatic hyperplasia which comprises administering to a mammal in need of said treatment a conjugate, said conjugate which comprises two cytotoxic agents attached to a oligopeptide, wherein the oligopeptide comprises a sequence of

amino acids that is recognized and selectively proteolytically cleaved by free prostate specific antigen, wherein the means of attachment is directly through a covalent bond or via a linker unit,

or the pharmaceutically acceptable salt thereof.

16. The method of treatment according to Claim 15 wherein the conjugate is



Compound 10

or the pharmaceutically acceptable salt thereof.

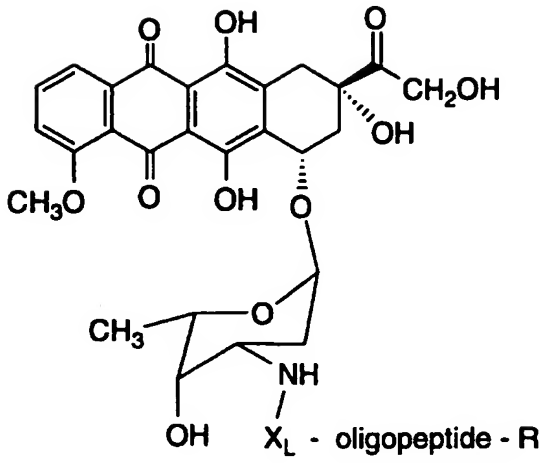
17. A pharmaceutical composition useful for treating an adverse condition of the prostate comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a conjugate, said conjugate which comprises a pharmaceutical agent, effective in the treatment of said condition, attached to a oligopeptide, wherein the oligopeptide comprises a sequence of amino acids that is recognized and selectively proteolytically cleaved by free prostate specific antigen, wherein the means of attachment is directly through a covalent bond or via a linker unit,

or the pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition useful for treating benign prostatic hyperplasia comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a conjugate, said conjugate which comprises a cytotoxic agent attached to a oligopeptide, wherein the oligopeptide comprises a sequence of amino acids that is recognized and selectively proteolytically cleaved by free prostate specific antigen, wherein the means of attachment is directly through a covalent bond or via a linker unit,

or the pharmaceutically acceptable salt thereof.

19. The composition according to Claim 18 wherein the conjugate is of the formula I:



I

wherein:

oligopeptide is an oligopeptide which is specifically recognized by the free prostate specific antigen (PSA) and is capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen;

X_L is absent or is an amino acid selected from:

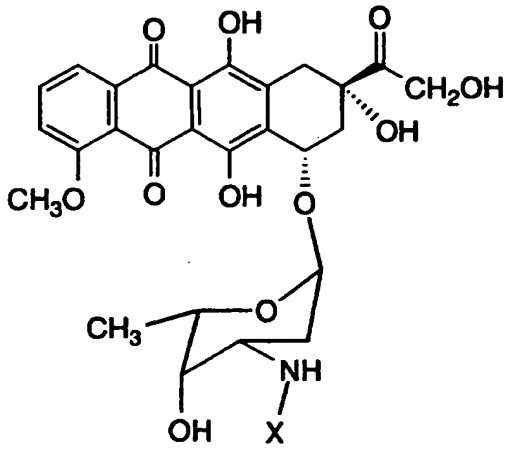
a) phenylalanine,
b) leucine,
c) valine,
d) isoleucine,
e) (2-naphthyl)alanine,
f) cyclohexylalanine,
g) diphenylalanine,
h) norvaline,
i) norleucine, and
j) 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;

R is hydrogen or $-(C=O)R^1$; and

R^1 is C_1-C_6-alkyl or aryl,

or the pharmaceutically acceptable salt thereof.

20. The composition according to Claim 18 wherein the conjugate is selected from:



wherein X is:

AsnLysIleSerTyrGlnSer— (SEQ.ID.NO.: 13),

AsnLysIleSerTyrGlnSerSer— (SEQ.ID.NO.: 16),

AsnLysIleSerTyrGlnSerSerSer — (SEQ.ID.NO.: 17),

AsnLysIleSerTyrGlnSerSerSerThr — (SEQ.ID.NO.:10),

AsnLysIleSerTyrGlnSerSerSerThrGlu — (SEQ.ID.NO.: 3),

AlaAsnLysIleSerTyrGlnSerSerSerThrGlu — (SEQ.ID.NO.: 11),

N-terminus

Ac—AlaAsnLysIleSerTyrGlnSerSerSerThr— (SEQ.ID.NO.: 117),

Ac—AlaAsnLysIleSerTyrGlnSerSerSerThrLeu— (SEQ.ID.NO.: 70),

Ac—AlaAsnLysAlaSerTyrGlnSerAlaSerThrLeu— (SEQ.ID.NO.: 118),

Ac—AlaAsnLysAlaSerTyrGlnSerAlaSerLeu— (SEQ.ID.NO.: 119),

Ac—AlaAsnLysAlaSerTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 120),

Ac—AlaAsnLysAlaSerTyrGlnSerSerLeu— (SEQ.ID.NO.: 121),

Ac—SerTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 144),

Ac—hArgTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 145),

Ac—LysTyrGlnSerSerSerLeu— (SEQ.ID.NO.: 124), or

Ac—LysTyrGlnSerSerNle— (SEQ.ID.NO.: 146),

↑
N-terminus

or the pharmaceutically acceptable salt thereof.

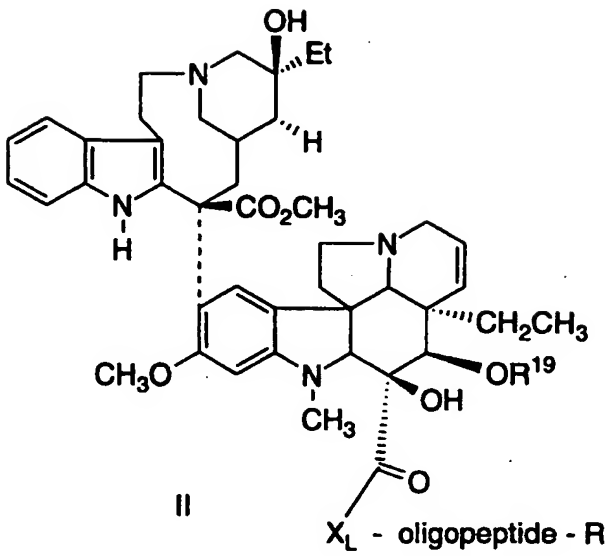
21. The composition according to Claim 18 wherein the conjugate is selected from:

Ac-hArgTyrGln-SerSerPro-dox(3') (SEQ.ID.NO.: 151)
Ac-hArgTyrGln-SerPro-dox(3') (SEQ.ID.NO.: 177)
Ac-hArgTyrGln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 154)
Ac-AmfTyrGln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 155)
H_2NCO-hArgTyrGln-SerSerSerLeu-dox(3') (SEQ.ID.NO.: 156)
Ac-LysTyrGln-SerSerNle-dox(3') (SEQ.ID.NO.: 146)

Ac-LysTyrGln-SerLysNle-dox(3') (SEQ.ID.NO.: 178)
Ac(cis-p-NH_2Cha)TyrGlnSerSerNledox(3') (SEQ.ID.NO.: 161)
Ac-AlaAspLysAla(hArg)TyrGln-SerSerLeu-dox(3') (SEQ.ID.NO.: 160)
Ac-hArgTyrGln-SerAsn-dox(3') (SEQ.ID.NO.: 153)
Ac-hArgTyrGln-SerSerHis-dox(3') (SEQ.ID.NO.: 152)
Ac-(imidazolyl)LysTyrGln-SerSerLeu-dox(3') (SEQ.ID.NO.: 159)
Ac-(imidazolyl)LysTyrGlnSerSerSerNle-dox(3') (SEQ.ID.NO.: 162)
Ac-hArg(Cha)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 163)
Ac-hArg(Me_2PO_3Tyr)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 167)
Ac-hArgTyrGln-SerSerSerhArg-dox(3') (SEQ.ID.NO.: 164)
Ac-hArg(3-Iodo-Tyr)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 166)
Ac-hArg(O-Me-Tyr)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 169)
Ac-hArg(p-NH_2-Phe)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 179)
Ac-hArg(Cha)Gln-SerSerNle-dox(3') (SEQ.ID.NO.: 174)
Ac-hArg(Cha)Gln-SerProNle-dox(3') (SEQ.ID.NO.: 175)
Ac(imidazolyl)Lys(Cha)GlnSerSerSerNle-dox(3') (SEQ.ID.NO.: 172)
Ac-hArg(7-HO-TIC)Gln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 180)
Ac-hArg(3-Fluoro)TyrGlnSerSerSerNle-dox(3') (SEQ.ID.NO.: 176)
Ac-(ornithine)TyrGln-SerSerSerNle-dox(3') (SEQ.ID.NO.: 181)
Ac-LysAlaAlaSerSerSerLeu-dox(3') (SEQ.ID.NO.: 183)
Ac-hArgh(Cha)Gln-SerSerNle-dox(3') (SEQ.ID.NO.: 149)
Ac-AlaArgLysAlaSerTyrGln-SerLeu-dox(3') (SEQ.ID.NO.: 193) and
Ac-(Orn)TyrGln-SerSerSerLeu-dox(3') (SEQ.ID.NO.: 194)

or the pharmaceutically acceptable salt thereof.

22. The composition according to Claim 18 wherein the conjugate is of the formula II:



wherein:

oligopeptide is an oligopeptide which is specifically recognized by the free prostate specific antigen (PSA) and is capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen;

X_L is absent or is an amino acid selected from:

a) phenylalanine,
b) leucine,
c) valine,
d) isoleucine,
e) (2-naphthyl)alanine,
f) cyclohexylalanine,
g) diphenylalanine,
h) norvaline,
i) norleucine, and
j) 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; or

X_L is - NH - $(CH_2)_n$ - NH -

R is hydrogen or -(C=O)R^1;

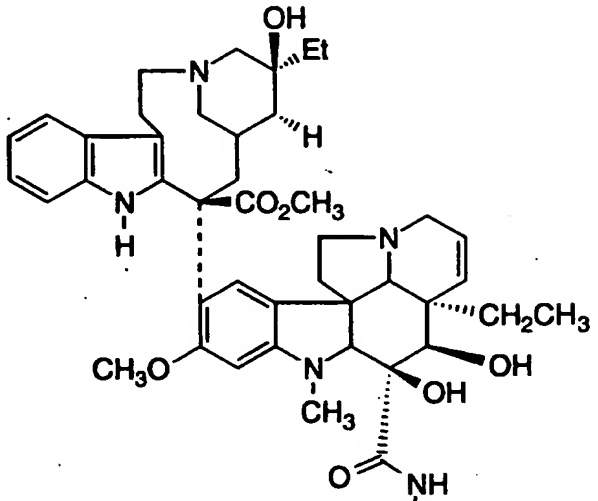
R^1 is C_1-C_6-alkyl or aryl;

R^{19} is hydrogen or acetyl; and

n is 1, 2, 3, 4 or 5,

or the pharmaceutically acceptable salt thereof.

23. The composition according to Claim 22 wherein the conjugate is:

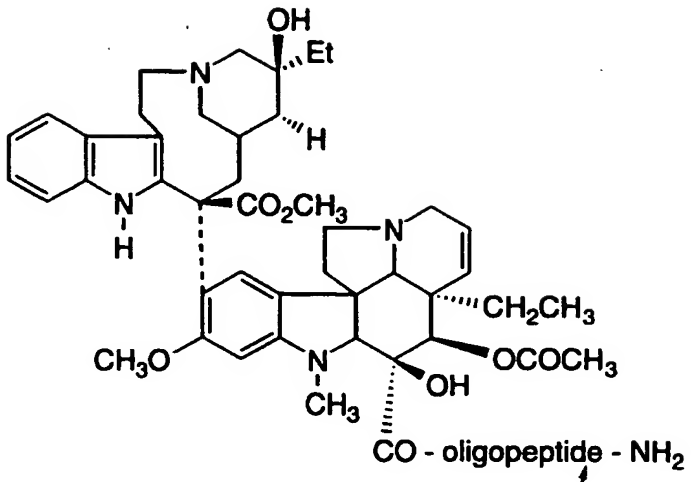


Compound 14

(SEQ.ID.NO.: 183),

or the pharmaceutically acceptable salt thereof.

24. The composition according to Claim 18 wherein the conjugate is of the formula II:



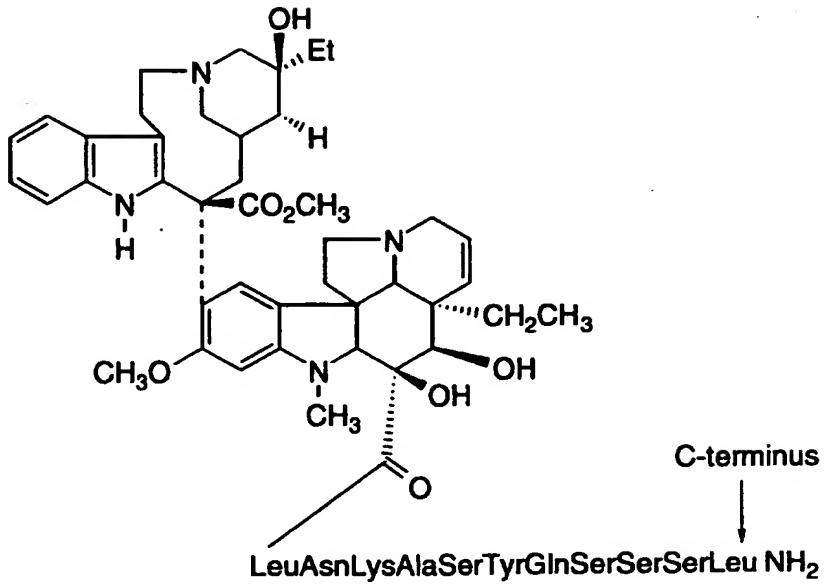
II

wherein:

oligopeptide is an oligopeptide which is specifically recognized by the free prostate specific antigen (PSA) and is capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen,

or the pharmaceutically acceptable salt thereof.

25. The composition according to Claim 24 wherein the conjugate is:



Compound 5 (SEQ.ID.NO.: 184),

or the pharmaceutically acceptable salt thereof.

26. A pharmaceutical composition useful for treating an adverse condition of the prostate which comprises administering to a mammal in need of said treatment a conjugate, said conjugate which comprises two pharmaceutical agents, wherein at least one pharmaceutical agent is effective against said condition, attached to a oligopeptide, wherein the oligopeptide comprises a sequence of amino acids that is recognized and selectively proteolytically cleaved by free prostate specific antigen, wherein the means of attachment is directly through a covalent bond or via a linker unit,

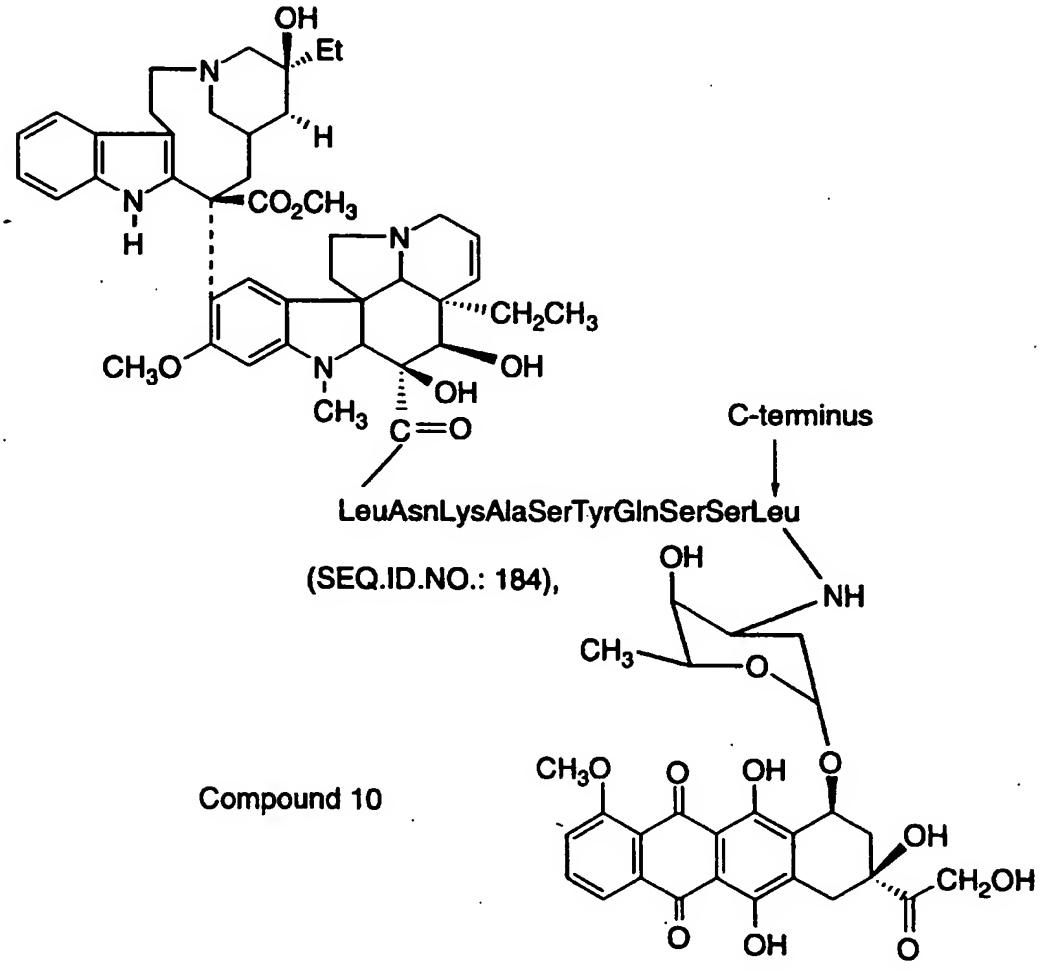
or the pharmaceutically acceptable salt thereof.

27. A pharmaceutical composition useful for treating benign prostatic hyperplasia comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a conjugate, said conjugate which comprises two cytotoxic agents attached to a

oligopeptide, wherein the oligopeptide comprises a sequence of amino acids that is recognized and selectively proteolytically cleaved by free prostate specific antigen, wherein the means of attachment is a covalent bond or a chemical linker,

or the pharmaceutically acceptable salt thereof.

28. The composition according to Claim 27 wherein the conjugate is



Compound 10

or the pharmaceutically acceptable salt thereof.

1: MetLysProAsnIleIlePheValLeuSerLeuLeuLeuIleLeuGluLysGlnAlaAla -

21: ValMetGlyGlnLysGlyGlySerLysGlyArgLeuProSerGluPheSerGlnPhePro -

41: HisGlyGlnLysGlyGlnHisTyrSerGlyGlnLysGlyLysGlnGlnThrGluSerLys -

61: GlySerPheSerIleGlnTyrThrTyrHisValAspAlaAsnAspHisAspGlnSerArg -

81: LysSerGlnGlnTyrAspLeuAsnAlaLeuHisLysThrThrLysSerGlnArgHisLeu -

101: GlyGlySerGlnGlnLeuLeuHisAsnLysGlnGluGlyArgAspHisAspLysSerLys -

121: GlyHisPheHisArgValValIleHisHisLysGlyGlyLysAlaHisArgGlyThrGln -

CS#5

141: AsnProSerGlnAspGlnGlyAsnSerProSerGlyLysGlyIleSerSerGlnTyr|Ser -

161: AsnThrGluGluArgLeuTrpValHisGlyLeuSerLysGlnGlnThrSerValSerGly -

181: AlaGlnLysGlyArgLysGlnGlyGlySerGlnSerSerTyrValLeuGlnThrGluGlu -

201: LeuValAlaAsnLysGlnGlnArgGluThrLysAsnSerHisGlnAsnLysGlyHisTyr -

221: GlnAsnValValGluValArgGluGluHisSerSerLysValGlnThrSerLeuCysPro -

241: AlaHisGlnAspLysLeuGlnHisGlySerLysAspIlePheSerThrGlnAspGluLeu -

261: LeuValTyrAsnLysAsnGlnHisGlnThrLysAsnLeuAsnGlnAspGlnGlnHisGly -

CS#3

281: ArgLysAlaAsnLysIleSerTyrGln|SerSerSerThrGluGluArgArgLeuHisTyr -

CS#4

301: GlyGluAsnGlyValGlnLysAspValSerGlnSerSerIleTyrSer|GlnThrGluGlu -

321: LysAlaGlnGlyLysSerGlnLysGlnIleThrIleProSerGlnGluGlnGluHisSer -

CS#1

341: GlnLysAlaAsnLysIleSerTyrGln|SerSerSerThrGluGluArgArgLeuHisTyr -

CS#2

361: GlyGluAsnGlyValGlnLysAspValSerGlnArgSerIleTyrSer|GlnThrGluLys -

381: LeuValAlaGlyLysSerGlnIleGlnAlaProAsnProLysGlnGluProTrpHisGly -

401: GluAsnAlaLysGlyGluSerGlyGlnSerThrAsnArgGluGlnAspLeuLeuSerHis -

421: GluGlnLysGlyArgHisGlnHisGlySerHisGlyGlyLeuAspIleValIleIleGlu -

441: GlnGluAspAspSerAspArgHisLeuAlaGlnHisLeuAsnAsnAspArgAsnProLeu -

461: PheThr -

FIG.1

PEPTIDE	PERCENT PEPTIDE HYDROLYSIS TIME OF INCUBATION (HOURS) 0.5	1	2	3	4	20
1. SYQSSSTE	ND	0	ND	0	ND	0
2. ISYQSSSTE	ND	0	ND	0	ND	0
3. KISYQSSSTE	ND	10	ND	30	ND	90
4. NKISYQSSSTE	ND	30	ND	70	ND	100
5. NKISYQSSST	ND	20	30	ND	ND	100
6. ANKISYQSSSTE	15	25	ND	ND	80	100
7. ANKISYQSSS	4	6	16	30	45	ND
8. NKISYQSSS	2	6	22	44	55	ND
9. ANKISYQSS	1	ND	12	ND	39	ND
10. GRKANKISYQS-SSTEERRLHYGENG	20	50	ND	ND	90	100

ND = NOT DETERMINED

FIG. 2

PEPTIDE	SALT	SEQ. ID. NO	% PEPTIDE CLEAVED AT 4 HRS BY YORK PSA
SEMENOGELIN (463 aa)			100 (30 MIN)
GRKANKISYQ-SSSTEERRLHYGENG	TFA	6	100 (2 HRS)
SQKANKISYQ-SSSTEERRLHYGENG	TFA	67	100 (3 HRS)
ANKISYQ-SSSTE	TFA	11	98
ISYQ-SSST	TFA	68	0
NKISYQ-SSST	TFA	10	62
NKISYQ-SSSTE	TFA	3	90
KISYQ-SSSTE	TFA	9	49
SYQ-SSSTE	TFA	7	0 (3 HRS)
ISYQ-SSSTE	TFA	8	0
NKISYQ-SSS	TFA	17	55
ANKISYQ-SSS	TFA	18	45
ANKISYQ-SS	TFA	69	39
ANKISYQ-SSSSTE-amide	TFA	11	43
Ac-ANKISYQ-SSSTL	TFA	70	57
Ac-ANKISYQ-SSSTE-amide	TFA	11	40
Ac-ANKISYQ-SSSTL-amide	TFA	70	46
Ac-ANGISYQ-SSSTE-amide		71	0
Ac-ANPISYQ-SSSTE-amide		72	0
Ac-ANKISYQ-SASTE-amide	TFA	73	66
Ac-ANKISYQ-SSKTE-amide	TFA	74	80
Ac-ANKISYQ-SSTE-amide	TFA	75	44
Ac-ANKI(dS)YQ-SSSTE-amide	TFA	76	9
Ac-ANK(dI)SYQ-SSSTE-amide	TFA	77	0
Ac-ANKISYQ-SSQTE-amide	TFA	78	55
Ac-ANKISYQ-SAKTE-amide	TFA	79	80
Ac-AN(dK)ISYQ-SSSTE-amide	TFA	80	3
Ac-ANKISYQ-STE-amide	TFA	81	28
Ac-ANKIYQ-SSTE-amide	TFA	82	0
Ac-ANKSYQ-SSTE-amide	TFA	83	10
Ac-ANKASYQ-SASTE-amide	TFA	84	98
Ac-ANEISYQ-SASTE-amide		85	10
Ac-NKISYQ-SS-amide	TFA	16	30
Ac-KISYQ-SS-amide	TFA	86	15
Ac-SYQ-SSTE-amide		87	65
Ac-SYQ-SSTL-acid		88	83
Ac-ASYQ-SSTE-amide		89	68
Ac-EISYQ-SSSTE-amide		90	0
Ac-ANEISYQ-SSSTE-amide		91	0

FIG.3

PEPTIDE	SALT	SEQ. ID. NO	% PEPTIDE CLEAVED AT 4 HRS BY YORK PSA
Ac-ANKISYY-SSSTE-amide	TFA	92	73
Ac-ANKISYY-SASTE-amide	TFA	93	91
Ac-ASYQ-SSL-acid		94	71
Ac-ANSYQ-SSSTE-amide		95	28
Ac-ASYQ-SSSTE-amide		96	64
Ac-SYQ-SSSTE-amide		97	50
Ac-ANKASYQ-SASTC-amide	TFA	98	78
Ac-Q-SSTE-amide		99	0
Ac-YQ-SSTE-amide		100	0
Ac-SQ-SSTE-amide		101	0
Ac-ANKISQ-SSTE-amide	TFA	102	0
Ac-AN(ORN)ISYQ-SSTE-amide	TFA	103	34
Ac-S(3 PAL)Q-SSTE-amide		104	4
Ac-S(3,4-C12F)Q-SSTE-amide		105	6
Ac-SKQ-SSTE-amide	TFA	106	0
Ac-SYQ-SSTL-acid		88	81
Ac-SYQ-SSSL-acid		107	98
(e-ACA)-YQ-SSSL-amide	AA	108	0
ANK(N-Me-I)SYQ-SSTE-amide	TFA	109	0
SYQ-SSTE-amide		110	0
HO(CH2)2CO-YQ-SSTE-amide		111	0
Ac-SYK-SSTE-amide	TFA	112	5
Ac-SYY-SSTE-amide		113	93
Ac-SYQ-SSL-NHNH2		114	32
Ac-SYQ-SSL-acid		115	72
DAP-YQ-SSSL-amide	AA	116	0

FIG.3A

PEPTIDE	SALT	SEQ ID NO	TIME TO CLEAVE 50% OF SUBSTRATE BY YORK PSA
SEMONOGELIN (463 aa)			100% AT 30 MIN
Ac-hR(Cha)Q-SNNle-acid	TFA	149	4 HR = 0% (PS)
Ac-hR(Cha)Q-SNle-acid	TFA	147	200 (PS)
Ac-hRhYQ-SSNle-acid	TFA	148	95 (PS)
Ac-ANKASYQ-SS-Cha-NHNH2	TFA	150	>240 (4 HR = 31%)
Ac-hRYQ-SSP-acid	TFA	151	30
hRYQ-SSH-acid	TFA	152	>240 (4 HR = 0%)
Ac-hRYQ-SSH-acid	TFA	152	60
hRYQ-SP-acid	TFA	177	>240 (4 HR = 0%)
Ac-hRYQ-SP-acid	TFA	177	>240 (4 HR = 0%
Ac-hRYQ-SN-acid	TFA	153	90
Ac-hRYQ-S-acid	TFA	187	>240 (4 HR = 0%)
Ac-hRYQ-SSSNle-acid		154	40
Ac-(Amf)YQ-SSSNle-acid		155	50
NH2CO-hRYQ-SSSL-acid	TFA	156	60
Ac-ANKAKYQ-SS(Cha)-NHNH2	TFA	157	240
Ac-(DPL)YQ-SSSNle-acid	TFA	158	120
Ac-(imidazolyl)KYQ-SSL-acid	TFA	159	25
Ac-ANKA(hR)YQ-SSL-acid	TFA	160	105
Ac-(p-NH2-Cha)YQ-SSSNle-acid	TFA	161	140
Ac-(imidazoyl)KYQSSSNle-acid	TFA	162	25
Ac-hR(Cha)Q-SSSNle-acid	TFA	163	120
Ac-hRYQ-SSShR-acid	TFA	164	70
Ac-hRYQ-SSS(MeL)	TFA	188	90
Ac-hRYQ-SSS(Ethylester-L)		156	85
Ac-ANKA(imidazolyl)KYQ-SSNle-acid	TFA	165	95
Ac-hR(3-Iodo-Y)Q-SSSNle-acid	TFA	166	55
Ac-hR(Me2PO3-Y)Q-SSSNle-acid	TFA	167	4 HR = 0%
Ac-hRYQ-SSD-acid	TFA	168	25
Ac-hR(O-Me-Y)Q-SSSNle-acid	TFA	169	4 HR = 0%
Ac-ANKAKYQ-SSNle-acid	TFA	170	80
Ac-hR(Cha)Q-SSS(ethylester-L)		171	4 HR = 36%
Ac-(imidazolyl)K(Cha)Q-SSSNle-acid	TFA	172	180 (PS)
Ac-hR(TIC)Q-SSSNle-acid	TFA	179	4 HR = 0%
Ac-Q-SSSNle-acid	TFA	189	4 HR = 0%
Ac-hR(Cha)Q-SSS-acid	TFA	173	120
Ac-hR(Cha)Q-SSNle-acid	TFA	174	60 (PS)
Ac-hR(Cha)Q-SPNle-acid	TFA	175	4 HR = 12%
Ac-hR(m-fluoro-Y)Q-SSSNle-acid	TFA	176	100
Ac-(7-HO-TIC)Q-SSSNle-acid	TFA	190	4 HR = 0%

FIG.3B

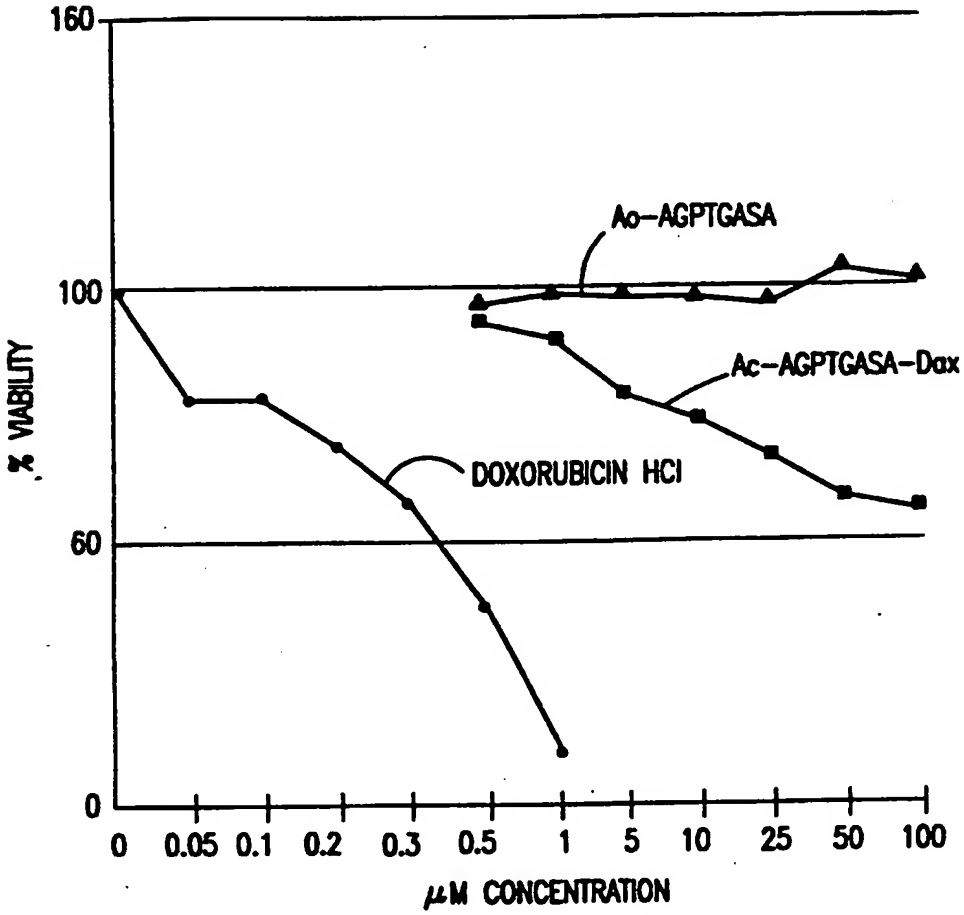

160
100
60
0
% VIABILITY
Ao-AGPTGASA
Ac-AGPTGASA-Dox
DOXORUBICIN HCl
0 0.05 0.1 0.2 0.3 0.5 1 5 10 25 50 100
μM CONCENTRATION

FIG.4

DOXORUBICIN-COGENER	SALT	SEQ. ID. NO.	% PEPTIDE CLEAVED AT 4 HOURS BY YORK PSA
Ac-ANKISYQ-SSST-DOX (3')	TFA	117	20(1 HR) NO SAMPLE LEFT
Ac-ANKISYQ-SSSTL-DOX (3')	TFA	70	87
Ac-ANKASYQ-SASTL-DOX (3')	AA	118	NA
Ac-ANKASYQ-SASL-DOX (3')	AA	119	100 (3 HR)
Ac-ANKASYQ-SSSL-DOX (3')	AA	120	100 (3 HR)
Ac-ANKASYQ-SSL-DOX (3')	AA	121	91
Ac-SYQ-SST(dL)-DOX (3')		122	17
Ac-SYQ-SSSL-DOX (3')		107	95 (PS)
Ac-ANKASYA-SSSL-DOX (3')	AA	123	0
Ac-KYQ-SSSL-DOX (3')	AA	124	98 (PS)
Ac-SYQ-SSKL-DOX (3')	AA	125	88
Ac-SYQ-SSK(dL)-DOX (3')	AA	126	87

FIG.5

DOXORUBICIN-COGENER	SALT	SEQ. ID. NO.	TIME TO CLEAVE 50% OF SUBSTRATE BY YORK PSA
Ac-(ORN)YQ-SSSNle-DOX (3')	AA	181	4 HR = 20%
Ac-KAASSSL-DOX (3')	AA	182	10X [ENZ] 20 HR = 11%
Ac-hRh(Cha)Q-SSNle-DOX (3')	AA	149	4 HR = 30%
Ac-hRYQ-SSP-DOX (3')		151	45
Ac-hRYQ-SP-DOX (3')		177	>240 (4 HR = 0%)
Ac-hRYQ-SSSNle-DOX (3')		154	190 (PS)
Ac-AmfYQ-SSSNle-DOX (3')		155	110 (PS)
NH2CO-hRYQ-SSSL-DOX (3')		156	105
Ac-KYQ-SSNle-DOX (3')	AA	146	>240 (4 HR = 36%) (PS)
Ac-KYQ-SKNle-DOX (3')	AA	178	>240 (4 HR = 20%) (NO PROD)
Ac-(cis-p-NH2Cha)YQSSNleDOX(3')		161	240 (PS)
Ac-ANKA(hR)YQ-SSL-DOX (3')		160	60
Ac-hRYQ-SN-DOX (3')	AA	153	90 (PS)
Ac-hRYQ-SSH-DOX (3')	AA	152	110
Ac-(imidazolyl)KYQ-SSL-DOX (3')		159	150
Ac-(imidazolyl)KYQSSSNle-DOX (3')		162	60
Ac-hR(Cha)Q-SSSNle-DOX (3')		163	130
Ac-hR(Me2PO3Y)Q-SSSNle-DOX (3')		167	4 HR = 0%
Ac-hRYQ-SSShR-DOX (3')		164	50
Ac-hR(3-Iodo-Y)Q-SSSNle-DOX (3')		166	4 HR = 0% (PS)
Ac-hR(O-Me-Y)Q-SSSNIE-DOX (3')		169	4 HR = 20% (PS)
Ac-hR(p-NH2-F)Q-SSSNle-DOX (3')		179	90 (PS)
Ac-hR(Cha)Q-SSNle-DOX (3')		174	120
Ac-hR(Cha)Q-SPNle-DOX (3')		175	4 HR = 0%
Ac(imidazolyl)K(Cha)QSSSNleDOX(3')		172	180
Ac-hR(TIC)Q-SSSNle-DOX (3')		180	4 HR = 14%
Ac-hR(3-Fluoro)YQSSSNleDOX (3')		176	4 HR = 26%
desAc-vinblastine-LNKASYQ-SSL-DOX	AA	184	70 (PS)
Ac-ANKASYQ-SL-DOX (3')	TFA	193	90
Ac-(ORN)YQ-SSSNle-DOX (3')	TFA	194	120

FIG.5A

DOXORUBICIN-CONGENER	SALT	SEQ. ID. NO.	% PEPTIDE CLEAVED/ LNCaP MEDIA 4 HR	% PEPTIDE CLEAVED/ DuPRO MEDIA 4 HR
Ac-ANKASYQ-SASL-DOX (3')	AA	119	92	13
Ac-ANKASYQ-SSSL-DOX (3')	AA	121	98	13
Ac-ANKASYQ-SSL-DOX (3')		122	95	27
Ac-SYQ-SSSL-DOX (3')		107	63	0

FIG.6

CYTOTOXIC AGENT-COGENER	SALT	SEQ.ID.NO	LNCaP CELL KILL EC50 (μM)
Ac-ANKISYQ-SSST-DOX(3')	TFA	117	>100
Ac-ANKISYQ-SSSTL-DOX(3')	TFA	70	8.4
Ac-ANKASYQ-SASTL-DOX(3')	AA	118	31
Ac-ANKASYQ-SASL-DOX(3')	AA	119	16 (DuPRO > 100)
Ac-ANKASYQ-SSSL-DOX(3')	AA	120	15
Ac-ANKASYQ-SSL-DOX(3')	AA	121	6.5 (DuPRO = 117)
Ac-SYQ-SSSL-DOX(3')		144	20 (DuPRO > 100)(PS)
Ac-ANKASYA-SSSL-DOX(3')	AA	191	>100
Ac-KYQ-SSSL-DOX(3')	AA	124	6.5 (DuPRO>100)(PS)
Ac-SYQ-SSKL-DOX(3')	AA	192	11.8 (DuPRO>100)
Ac-SYQ-SSK(dL)-DOX(3')	AA		>100 (DuPRO>100)
Ac-hRYQ-SSSL-DOX(3')	AA	145	6.4 (DuPRO>100)
Ac-KYQ-SSSNle-DOX(3')	AA	183	4.4 (DuPRO>100)
Ac-(ORN)YQ-SSSNle-DOX(3')	AA	181	3.3 (DuPRO = 65)
Ac-hRh(Cha)Q-SSNle-DOX(3')	AA	149	
o-Me-A-DX(3')	AA		7.0 (DuPRO = 20.8)
M-DOX(3')	AA		6.0 (DuPRO = 13.8)
			{4.9(DuPRO = 33.3)}
G-DOX(3')	AA		>100 (DuPRO>100)
N-methyl-G-DOX(3')	AA		39.0 (DuPRO = 58.8)
NH2(CH2)5-CO-DOX(3')	AA		59.2 (DuPRO > 100)
Ac-hRYQ-SSP-DOX(3')		151	{33.3(DuPR=100)}
Ac-hRYQ-SP-DOX(3')		177	25.2 (DuPRO = 44.5)
Ac-hRYQ-SSSNle-DOX(3')		154	4.4(DuPRO = 41.0)(PS)
Ac-AmfYQ-SSSNle-DOX(3')		155	7.6(DuPRO>100)(PS)
NH2CO-hRYQ-SSSL-DOX(3')		156	35.7 (DuPRO>100)
Ac-KYQ-SSNle-DOX(3')	AA	146	4.6(DuPRO = 76.9)(PS)
Ac-KYQ-SKNle-DOX(3')	AA	178	5.7(DuPRO>>100){3.6}
Ac-(cis-p-NH2Cha)YQSSNleDOX(3')		161	9.8(DuPRO = 47.1)(PS)
Ac-ANKA(hR)YQ-SSL-DOX(3')		160	7.3(DuPRO>>100)
AchRYQ-SN-DOX(3')	AA	153	70.4(DuPRO = 75.0)
Ac-hRYQ-SSH-DOX(3')	AA	152	25.4 (DuPRO = 35.7)
Ac-(imidazolyl)KYQ-SSL-DOX(3')	AA	159	6.3(DuPRO = 12.8)(PS)
Ac-(imidazolyl)KYQSSSNle-DOX(3')		162	3.2 (DuPRO = 23) (PS AT 50 mM)
Ac-hR(Cha)Q-SSSNle-DOX(3')		163	2.3 (DuPRO >>100)
Ac-hR(Me2PO3Y)Q-SSSNle-DOX(3')		167	8.0 (DuPRO>100)
Ac-hRYQ-SSShR-DOX(3')		164	32 (DuPRO>100)
Ac-hR(3-Iodo-Y)Q-SSSNle-DOX(3')		166	12.8 (DuPRO = 60.8)
Ac-hR(O-Me-Y)Q-SSSNle-DOX(3')		169	7.4 (DuPRO = 13.5)

FIG.7

CYTOTOXIC AGENT-COGENER	SALT	SEQ. ID. NO	LNCaP CELL KILL
			EC50 (μM)
Ac-hR(p-NH2-F)Q-SSSNle-DOX(3')		179	7.5 (DuPRO>100)
Ac-hR(Cha)Q-SSNle-DOX(3')		174	3.4 (DuPRO>100)
Ac-hR(Cha)Q-SPNle-DOX(3')		175	12.3 (DuPRO>100)
Ac-ANKASYQ-SL-DOX(3')	TFA	193	10 (DuPRO>100)
Ac-(ORN)YQ-SSSNle-DOX(3')	TFA	194	7.0 (DuPRO>100)
Ac-(imidazolyl)K(Cha)QSSSNleDOX(3')		172	4.0 (DuPRO>100) (PS)
Ac-hR(TIC)Q-SSSNle-DOX(3')		180	3.2(DuPRO = 50.9)
Ac-hR(3-Fluoro)YQSSSNleDOX(3')		176	3.2(DuPRO = 58.8)
vinblastine			0.5(DuPRO = 85)
DAP-desAc-vinblastine	TFA		150 (DuPRO>>100)
Ac-KYQ-SSSNle-DAP-desAc-vinblastine	TFA	183	14.7(DuPRO>>100) {4.8}
Nle-DAP-desAc-vinblastine	TFA		5.9(DuPRO>100)
desAc-vinblastine-LNKASYQ-SSSL-amide	AA	184	1.6(DuPRO>>100)

FIG.7A

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/16490

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/40, 31/44, 31/70, 38/02, 38/07, 38/08, 38/10, 38/14
US CL :514/2, 8, 14, 15, 16, 17, 18, 34, 283
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 8, 14, 15, 16, 17, 18, 34, 283; 530/300, 322, 327, 328, 329, 330

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, DIALOG
search terms: prostate, psa, protease, cleavage, proteolysis, substrate, hyperplasia, conjugate, linker

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US 5,501,983 A (LILJA ET AL) 26 March 1996 (26.03.96), see column 1, lines 13-37.	1-28
A,P	US 5,502,037 A (A. KONDRATYEV) 26 March 1996 (26.03.96), see column 5, lines 36-48, column 6, lines 44-62.	1-28
X,P	WO 96/00503 A1 (MERCK & CO., INC.) 11 January 1996 (11.01.96), see entire document, especially page 20, line 20 - page 21, line 9, claims 12-20.	1-12, 17-22, 24
A	US 5,349,066 A (KANEKO ET AL) 20 September 1994 (20.09.94).	1-28
A	US 5,391,723 A (J. PRIEST) 21 February 1995 (21.02.95).	1-28

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
03 DECEMBER 1996	31 JAN 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEFFREY E. RUSSEL Telephone No. (703) 308-0196

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